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EFFECT OF CINCHOPHEN ON SECRETION OF CHOLIC ACID

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CHICAGO

Those investigators who have observed damage to the liver after administration of cinchophen to laboratory animals used doses at least ten times the equivalent dose for human beings estimated on the basis of body weight.[1] Those who have used the same or smaller doses failed to find any striking evidence of hepatic damage [2] or of depression of hepatic function.[3] Stalker, Bollman and Mann [4] gave twice the average human dose to a relatively large number of dogs for periods up to thirty-nine weeks. Although they observed gastrointestinal intolerance, which usually subsided, they did not observe jaundice or microscopic evidence of pathologic changes in the liver and other tissues, other than "peptic ulcer."

It was believed that if cinchophen has a direct toxic effect on the liver it should be manifested by a disturbance of secretion of cholic acid, since the output of that substance is readily affected by an infectious or toxic hepatitis. In a previous publication we [2c] failed to observe any significant decrease in secretion of cholic acid when 1 Gm. of the drug was given by mouth daily for three days up to thirty days. However, in all but 1 of the experiments the bile drained to the outside into a bag and from 60 to 75 per cent of the orally administered cinchophen was recovered in the bile in the bag. It was thought that if the administered cinchophen was permitted to undergo continuous enterohepatic circulation evidence of disturbance of secretion of cholic acid might result.

METHODS

The Preparation of the Animals. — Dogs weighing from 10 to 12 Kg. were prepared with chronic biliary fistulas by the method of Kocour and Ivy.[5] A small tube was inserted into the duodenum which led to the outside of the dog through a stab wound in the abdomen for the return of bile to the dog's intestine. Thus the bile could be collected hourly, and a small sample (0.1 cc.) could be withheld for estimation of cholic acid [6] and the remainder returned to the duodenum.

All the anmials had been operated on at least one month previously and had been maintained on a standard diet from that time to the beginning of these experiments. Previous to, and during experiments, the daily ration was divided into three portions and fed every eight hours.

The Dose of Cinchophen.—The dose of the drug employed in treatment of gout ranges from 7.5 to 30 grains (0.5 to 2 Gm.) daily, or from 7 to 28 mg. per kilogram of body weight for a patient weighing 70 Kg.[14] A dose of 7.5 grains (0.5 Gm.) three or four times daily for three consecutive days each week is the dose most recently recommended.[7] Some use 45

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1. (*a*) Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **28**:581, 1930. (*b*) Knoble, R. M., and Smith, H. A.: The Effect of Cinchophen on the Liver of White Rats, Am. J. Physiol. **97**:537, 1931. (*c*) Barbour, H. G., and Fisk, M. E.: Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, J. Pharmacol. & Exper. Therap. **48**:341, 1933. (*d*) Lehman, A. J., and Hanzlik, P. J.: Cinchophen Toxicosis, Arch. Int. Med. **52**:471 (Sept.) 1933. (*e*) Radwin, L. S., and Lederer, M.: Effect of Cinchophen on the Albinic Rat, Arch. Path. **15**:490 (April) 1933.

2. (*a*) Reichle, H. S.: Cinchophen Poisoning: An Attempt to Produce Toxic Cirrhosis of the Liver in Rats, Arch. Int. Med. **49**:215 (Feb.) 1932. (*b*) Barbour, H. G., and Gilman, A.: Cinchophen and Tolysin: Comparison of Effects of Administration of Each in Rats, J. Pharmacol. & Exper. Therap. **55**:400, 1935. (*c*) Berman, A. L.; Sharp, E.; Atkinson, A. J., and Ivy, A. C.: Effect of Cinchophen on Bile Formation, J. Lab. & Clin. Med. **28**:682, 1943.

3. Furth, O., and Scholl, R.: Biochemical Studies on Mechanism of Phenylcinchoninic Intoxication, J. Lab. & Clin. Med. **18**:991, 1933. Myers, H. B., and Goodman, L.: Cinchophen Hepatitis, Arch. Int. Med. **49**: 946 (June) 1932. Churchill and Van Wagoner.[1a] Lehman and Hanzlik.[1d]

4. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Effect of Cinchophen on the Liver and Other Tissues of the Dog, Proc. Soc. Exper. Biol. & Med. **35**:158, 1936.

5. Kocour, E. J., and Ivy, A. C.: The Effect of Certain Foods on Bile Volume Output in the Dog by a Quantitative Method, Am. J. Physiol. **122**:325, 1938.

6. Reinhold, J. G., and Wilson, D. S.: The Determination of Cholic Acid in Bile, J. Biol. Chem. **96**: 637, 1932.

7. Hench, P. S.: Diagnosis and Treatment of Gout and Gouty Arthritis, J. A. M. A. **116**:453 (Feb. 8) 1941.

grains (3 Gm.) daily, which is 42 mg. per kilogram for a patient weighing 70 Kg.[8] In order to be more certain of obtaining effects from the drug, we chose to give from 50 to 100 mg. per kilogram of body weight daily.

The cinchophen used was snow white, free of the odor of phenolquinoline and completely soluble in alkaline aqueous solution (Calco Company). It was a purer product than the cinchophen on the market and was used by us several years ago in other experimental work.[9]

The Plan of the Experiments.—I. The animals were placed on the standard diet and fed every eight hours without return of bile. This was to obtain control data regarding their basal synthesis of cholic acid so that the effect of cinchophen on it could be determined.[2c] II. Then bile was returned hourly without any change in feeding. This procedure was to obtain control data to compare with the observations made with the same regimen plus administration of cinchophen. III. Procedure II was then repeated with administration of cinchophen. IV. Finally, the administration of cinchophen and the return of bile were stopped and the cholic acid synthesis with the diet alone was again determined during the next three or four days. These data were obtained to supply information showing whether cinchophen had disturbed the cholic acid-synthesizing mechanism of the liver.

TABLE 1.—*Data Showing Slight Effect of 0.5 Gm. of Cinchophen (T 1) Every Twelve Hours and 0.25 Gm. Every Six Hours (T 2) on Secretion of Cholic Acid* *

Dog A3

	Volume of Bile in Cc.‡			Cholic Acid Output in Mg.		
Hours †	C	T1	T2	C	T1	T2
6	50	64	71	631	768	1,713
12	70	94	120	1,734	2,174	2,411
18	92	124	128	2,621	2,362	3,640
24	77	126	112	2,141	2,994	3,538
30	107	154	139	2,962	2,894	3,771
36	119	131	175	3,743	4,634	4,289
42	127	143	162	4,300	4,121	3,815
48	130	104	175	4,350	2,043	5,102
Total	762	880	1,082	23,482	21,990	28,279
48-00	65	90	90	673	Trace	1,265

* Except during the last six hours of test 1.
† The hourly outputs of volume and cholic acid are added to give the six hour total.
‡ This dog is unusual in the large amount of cholic acid synthesized and secreted. C, control, bile returned hourly without drug; T1, 0.5 Gm. of cinchophen given every twelve hours; T2, 0.25 Gm. of cinchophen given every six hours.

RESULTS

Sixteen experiments were performed on 8 dogs.

Since the animals responded differently at different times, the results for each animal will be summarized. Because it is impractical to submit all of the hourly data, only portions will be shown and the remainder will be condensed as averages.

Dog 1 (A3).—When 0.5 Gm. of the drug was given every twelve hours (test 1, table 1), the secretion of cholic acid was not affected until six hours after the third dose. The effect increased so that during the first six hours after completion of the hourly return the bile contained only traces of cholic acid. It should be noted that a part of the forty-eight hour meal was refused. Appetite and output of cholic acid then returned to normal. On referring to column 4, table 4, it will be seen that basal synthesis of cholic acid was not disturbed after the animal recovered from the twelve hours of depression of secretion of cholic acid. The dose of 0.25 Gm. every six hours (table 1, test 2), given one week after the first experiment, did not depress the output of cholic acid or affect the gastrointestinal tract as judged by objective symptoms. In fact, it would appear that the output of cholic acid was increased above the control level, the forty-eight hour output being 20 per cent above the forty-eight hour control value.

Dog 2 (B3).—This animal after receiving the first dose of 0.5 Gm. of the drug manifested the usual increment in output of cholic acid which follows hourly return of bile. However, at eighteen hours the output decreased, and just prior to twenty-four hours vomiting and diarrhea occurred. The animal refused food thereafter. Administration of the drug was continued, however, until four doses had been given, and the bile was returned hourly. The output of cholic acid was low, and only traces were present during the thirty-eighth and thirty-ninth hours. When return of bile was stopped, the output of cholic acid was so low that it could not be accurately estimated, which shows that the animal did not synthesize cholic acid and did not excrete the cholic acid absorbed from the intestine. Diarrhea had disappeared. The animal continued to refuse food, though the liver recovered sufficiently to synthesize that amount of cholic acid which occurs during fasting in a healthy fistula dog. The animal died the fifth day after the experiment, and autopsy revealed only gastroenteritis.

This observation indicates that it is hazardous to continue administration of cinchophen after manifestation of the symptoms of gastrointestinal irritation.

Dog 3 (D6).—Four tests were performed on this animal (table 2). In the first test, in which a dose of 0.5 Gm. every twelve hours was used, the output of cholic acid was depressed during the first sixteen hours, again during the twenty-first and twenty-second hours, and again during the twenty-ninth and fortieth hours. The output of cholic acid for the entire period with cinchophen was 37 per cent less than that for the control period. Synthesis of cholic acid was not affected during the post-treatment basal period following this test (table 4).

During the second test, one week later, the same dose of cinchophen was used with 1 Gm. of calcium gluconate. The output of cholic acid during the test was 13 per cent less than the control value, though a definite depression occurred at no time during the test. The post-treatment basal synthesis of cholic acid was within the normal range.

In the third test, several weeks after the second, 0.25 Gm. of the drug was given every twelve hours. The output of cholic acid during the period was 9 per cent above the control level.

In the fourth test, performed several weeks after the third, 1 Gm. of the drug was given every twenty-four hours for two days, 2 Gm. of calcium gluconate being given with the second dose of the drug in an

8. New and Nonofficial Remedies, Chicago, American Medical Association Press, 1941.

9. Reid, P. E., and Ivy, A. C.: Gastric Mucin a Prophylactic Against Gastro-Intestinal Ulcers and "Acute" Toxicity Resulting from Cinchophen, Proc. Soc. Exper. Biol. & Med. **34**:142, 1936.

effort to observe a difference in cholic acid response when the calcium was given. The output of cholic acid was greater than the control value throughout the forty-eight hour period, and the total output was 25 per cent greater. The post-treatment synthesis of cholic acid was about the normal value for basal conditions with diet alone (table 4).

Dog 4 (C4).—This animal received cinchophen on three occasions. The output of cholic acid was depressed for two hours after the first dose of cinchophen (0.5 Gm. every twelve hours). After that the output remained at or slightly above the control level (table 4); the same was true for basal synthesis of cholic acid with the diet, after administration of cinchophen was stopped.

Two weeks later the first dose of cinchophen was repeated, except that 1 Gm. of sodium bicarbonate was given with each dose. The output of cholic acid was markedly depressed (table 3) for the first twelve hours and in the twenty-eighth hour of the test. During the last twelve hours of the forty-eight hour period, the output was so markedly increased that the total for the forty-eight hour period was only 14 per cent below the control value (table 4). Synthesis during the post-treatment period was not influenced (table 4).

Six weeks after the first test, the same procedure was repeated with the same dose of cinchophen without sodium bicarbonate. No depression of output or synthesis of cholic acid during this test or during the post-treatment period occurred.

Dog 5 (D7).—Two tests were performed on this animal, one with the 0.5 Gm. dose and one with a 0.25 Gm. dose every twelve hours. With the 0.5 Gm. dose no depression of output of the cholic acid occurred at any time; in fact, 18 per cent more cholic acid was secreted during the forty-eight hour test period than during the forty-eight hour control period. Several weeks later with the 0.25 Gm. dose a depression occurred during the third hour and from the eighth to the eleventh hour after the first dose (table 3). This depression, however, was more than compensated for later in the test period, since the total output of cholic acid for the test was 12 per cent above the control value. The post-treatment basal synthesis of cholic acid was not affected in either test.

It is interesting to note that this animal was affected more by a dose of 250 mg. of the drug than by 500 mg. and that depression occurred the second time the animal was subjected to the influence of cinchophen but not the first time.

Dog 6 (D4).—This animal first received a dose of 0.25 Gm. of cinchophen and two weeks later a dose of 0.5 Gm. every twelve hours.

TABLE 2.—*Results of Four Tests on the Same Dog*

Dog D6

	Volume in Cc.†					Cholic Acid in Mg.				
Hour *	C	T1	T2	T3	T4	C	T1	T2	T3	T4
6	24	44	52	40	27	183	Trace	351	333	231
12	44	60	88	71	47	457	169	762	836	610
18	49	87	80	90	82	743	309	677	1,154	1,152
24	60	73	75	78	110	1,185	577	861	1,323	1,409
30	60	75	65	66	123	1,142	795	1,072	1,090	1,540
36	64	92	107	82	95	1,055	976	843	1,246	1,638
42	55	105	106	72	118	971	919	1,052	1,181	1,470
48	74	89	81	62	116	1,711	927	852	987	1,258
Total	420	625	654	561	719	7,447	4,672	6,470	8,150	9,308
54 ‡	37	28	48	34	60	830	391	478	599	495
60	29	31	35	25	37	320	Trace	152	250	152
72	28	61	59	64	62	256	537	320	...	279
Total	514	745	796	684	878	8,853	5,600	7,420	...	10,234

* Hourly outputs of volume and cholic acid are added to give six hour values.
† C, control, bile returned hourly without drug; T1, 0.5 Gm. of cinchophen every twelve hours; T2, 0.5 Gm. of cinchophen every twelve hours plus 1 Gm. of calcium gluconate; T3, 0.25 Gm. of cinchophen every twelve hours; T4, 1.0 Gm. of cinchophen every twenty-four hours.
‡ Hourly return of bile stopped at forty-eight hours.

TABLE 3.—*Output of Cholic Acid During the First Twelve Hours of the Control and After the First Dose of Cinchophen with Hourly Return of Bile* *

	Mg. Cholic Acid †									
	Dog A3		Dog B3	Dog C4		Dog D7		Dog D4		Dog D6	
Hour	C	T1	T1	C	T2 ‡	C	T2 ‡	C	T1	C	T1
1	45	43	77	8	Trace	10	70	6	Trace	10	4
2	87	110	120	15	Trace	25	44	22	Trace	21	Trace
3	121	110	86	25	Trace	34	Trace	43	4	35	Trace
4	132	131	71	8	Trace	28	59	26	12	35	Trace
5	182	166	86	34	Trace	65	103	54	7	43	Trace
6	84	231	100	22	34	41	130	72	6	41	Trace
7	344	202	144	34	Trace	34	130	108	Trace	58	Trace
8	195	259	264	105	31	86	Trace	77	13	83	Trace
9	336	344	373	95	Trace	28	Trace	39	31	10	Trace
10	313	483	390	136	Trace	105	Trace	73	47	95	Trace
11	168	529	344	158	Trace	63	141	73	57	92	94
12	328	357	305	165	Trace	88	72	81	39	119	75
Total	2,365	2,942	2,360	803	116	607	749	674	216	1,169	169

* Only those dogs that were affected by the cinchophen are listed. The marked depression in dogs A3 and B3 was not manifested the first twelve hours. No control was made on B3.
† C, control, bile returned hourly without drug; T1, first test of dog with cinchophen; T2, second test with cinchophen; A3, B3, C4 and D6 received 0.5 Gm. of cinchophen every twelve hours; D4 and D7 received 0.25 Gm. of cinchophen every twelve hours.
‡ One gram of sodium bicarbonate was given with the cinchophen.

During the first test the output of cholic acid was depressed during the first fourteen hours (table 3); later recovery occurred, so that the total decrease in output for the period was 28 per cent. During the post-treatment period, basal synthesis of cholic acid with the diet alone was greater than during a control period under similar conditions.

During the second test, with 0.5 Gm. of cinchophen, the output of cholic acid was not depressed at any time; during the test with the drug 48 per cent more cholic acid was secreted than during the control test (table 4).

Dog 7 (D8).—One experiment was performed in which 250 mg. of cinchophen was given the twelfth hour and 500 mg. the twenty-fourth hour of return of bile. The output of cholic acid was not depressed after the drug was given or in the post-treatment period.

Dog 8 (E6).—One experiment was done, in which 125 mg. of cinchophen was given the twelfth, twenty-fourth and thirty-sixth hours of return of bile. The output of cholic acid was not depressed after administration of the drug was started. There was no post-treatment depression of the output under basal conditions with the diet alone.

TABLE 4.—*Summary of Results*

Dog	A Cholic Acid Basal on Diet Alone,* Range in Mg.	I Predrug Cholic Acid Basal Control in Mg.	II Control Bile Returned Hourly, No Drug (Mg.)	III Test; as II; with Drug (Mg.)	Per Cent of Change Referred to II	IV Postdrug Cholic Acid (Compare with A and I [Mg.])	Dose of Drug
A3	1,400-2,000 (10 tests)	1,437	23,482	21,990	— 6	1,613	0.5 Gm. b. i. d.
		1,675	23,482	29,279	+20	1,722	0.25 Gm. q. i. d.
B3†	.....	1,547	.....	5,664	....	910†	0.5 Gm. b. i. d.
C4	980-1,700 (6 tests)	985	9,145	10,026	+ 9	1,243	0.5 Gm. b. i. d.
		1,567	9,145	7,876	+14	1,610	0.5 Gm. b. i. d.‡
		1,515	9,145	9,948	+ 8	1,412	0.5 Gm. b. i. d.
D7	1,100-2,400 (4 tests)	2,360	6,071	8,664	+18	2,710	0.5 Gm. b. i. d.
		1,090	6,071	7,181	+12	1,500	0.25 Gm. b. i. d.
D4	1,400-1,800 (3 tests)	2,000	5,757	4,158	—28	2,500	0.25 Gm. b. i. d.
		1,704	5,757	8,548	+48	.....	0.5 Gm. b. i. d.
D6	900-1,400 (4 tests)	1,013	7,447	4,672	—37	950	0.5 Gm. b. i. d.
		1,312	7,447	6,470	—13	1,252	0.5 Gm. b. i. d.‖
		950	7,447	8,150	+ 9	1,070	0.25 Gm. b. i. d.
		773	7,447	9,308	+25	762	1.0 Gm. every 24 hours ‖
D8	1,824 (4 tests)	1,950	.....	20,599	....	1,865	0.750 Gm. b. i. d.
E6	1,650 (3 tests)	1,335	.....	15,946	....	1,332	0.125 Gm. b. i. d.

* Each test is the average of 3 days' basal output on diet alone.
† This animal refused food during this test and hence the output represents the fasting synthesis of cholic acid. The animal died as a result of the test; no other tests were made previous to this one.
‡ 1.0 Gm. sodium bicarbonate was given with the drug.
‖ 1.0 Gm. of calcium gluconate was given with each dose of the drug.

COMMENT

A temporary depression in output of cholic acid was observed in six out of the 8 dogs in this study. Depression occurred with doses of 0.25 Gm. every twelve hours as well as with 0.5 Gm. every twelve hours. In the 16 tests on 8 dogs, definite depression occurred at some time during the forty-eight hour period of administration of the drug and hourly return of bile in 6, or 38 per cent, of the tests. In 4 of these 6 tests depression occurred chiefly after the first dose of the drug. In 1 test depression occurred only after the third dose, and in the other it occurred after two doses. The depression was sufficiently great or prolonged to influence the total forty-eight hour output in only 4 tests, or 25 per cent. It is important to realize that if hourly analyses for cholic acid had not been made, depression of the output would have been discovered in only 4 tests. In 1 dog depression of secretion of cholic acid occurred during the second administration of cinchophen and not during the first test with the drug (C4, table 4).

Anorexia occurred in only 2 instances. In 1 (A3, test 1) it was probably in part responsible for the late decrease in output of cholic acid, since formation of cholic acid probably depends on metabolism of protein. In the other case the animal manifested vomiting and diarrhea after the second dose of cinchophen and refused all food until death occurred the fifth day after the completion of the forty-eight hour test. This shows that a definite disturbance of appetite, although a good indication that the liver is affected to the extent that a decrease in output of cholic acid occurs, is not an entirely reliable criterion. Except for analysis of the bile for cholic acid, it is the best criterion that we have observed in these 8 animals and in 10 others which we have studied but which are not mentioned in this report because an hourly enterohepatic circulation of bile and cinchophen was not established.

In 2 and possibly 3 tests (dogs A3, D4 and D6, table 4), the output of cholic acid was increased with administration of cinchophen. We cannot be certain of this, however, since the hourly return of bile during a forty-eight hour period leads to a more rapid accumulation of cholic acid in the enterohepatic circuit at some times than at other times in the same dog. That this irregularity of accumulation of cholic acid

does not explain the depression seen in 6 dogs is apparent from the tables. The output of cholic acid was almost completely suppressed for periods of several hours with cinchophen, which differs from the more steady and less marked depression which may appear to occur in some of a series of tests on any single dog. Observations made in other work [10] show that the rate of accumulation of cholic acid in the enterohepatic circuit may vary as much as 15 per cent from test to test in the same animal. Hence, we doubt the significance of any increase smaller than 20 per cent under the conditions of these experiments.

We were especially interested in ascertaining whether forty-eight hours of administration of cinchophen would affect the liver in relation to synthesis of cholic acid from the protein in the diet. The data (table 4, column 4) reveal that in the period from twenty-four to seventy-two hours after the termination of the administration of the drug, synthesis of cholic acid was not significantly altered. In 3 instances the output of cholic acid was depressed when return of bile and administration of cinchophen were stopped at the end of forty-eight hours for from two to twelve hours, but the return to the normal level was prompt thereafter. In 1 of these tests, on B3, the animal that died, the synthesis which occurred after the marked depression due to the drug was a high normal value for fasting. Synthesis occurred even up to the hour of death. The sample of bile in the collecting cylinder when the animal died contained a normal amount of cholic acid for the fasting condition.

Recovery of synthesis and output of cholic acid after administration of the drug has been discontinued might be anticipated, since in a subsequent study it will be shown that the bile becomes free of cinchophen in fifteen to twenty-four hours after administration of the last of a series of doses from 0.250 Gm. up to 1 Gm. daily with return of the bile to the intestine hourly. However, recovery of output of cholic acid will occur (tables 3 and 4) after it has been initially depressed by cinchophen even while the administration of the drug is continued. This fact, together with the fact that dog B3 died when the liver had been free of exposure to cinchophen for five days, indicates that the drug may in some instances injure some vital function of the liver unrelated to the synthesis and excretion of cholic acid.

10. Berman, A. L.; Snapp, E.; Ivy, A. C., and Atkinson, A. J.: On the Regulation and Homeostasis of the Cholic Acid Output in Biliary Fistula Dogs, Am. J. Physiol. **131**:776, 1941.

On the contrary, it may be argued that gastroenteritis was the cause of death of dog B3 and not hepatic damage due to the cinchophen. It may also be argued that the suppression of secretion of cholic acid observed for short periods on some occasions in dogs other than B3 was due to a disturbance of digestion and absorption of protein. Since we did not analyze the stools for nitrogen, this possibility cannot be answered by submission of direct evidence. However, as is well known, the liver of the fasting dog synthesizes and secretes cholic acid, and it is difficult to believe that cinchophen would so alter the intestine that none or only traces of the cholic acid in the bile initially returned to the intestine would be absorbed. So we attribute the marked depression in secretion of cholic acid, when observed, to an effect of the cinchophen on the hepatic cells.

In the 3 tests in which sodium bicarbonate or calcium gluconate was given with the cinchophen, the volume output or cholic acid content of the bile was not modified significantly. In test 2 on dog C4, in which sodium bicarbonate was given, cinchophen initially depressed the output of cholic acid (table 3). This evidence supports the view that the suppression of secretion of cholic acid, when it occurs, is not due solely to gastrointestinal irritation.[11]

SUMMARY AND CONCLUSIONS

Doses of cinchophen which on the basis of body weight are from one to four times the dose recently suggested for the use in the management of gout in human beings [7] and which in the past have failed to cause disturbance in hepatic liver function as studied by the ordinary tests [1d] may sometimes cause a marked temporary depression of synthesis and secretion of cholic acid by the livers of dogs. After such doses of cinchophen a complete temporary suppression of secretion of cholic acid may occur in the absence of anorexia and objective gastrointestinal symptoms.

Most animals recover from the suppression of synthesis and secretion of cholic acid during repeated administration of cinchophen in the doses used.

Since 1 extremely susceptible animal in our series recovered from the suppression of synthesis and secretion of cholic acid and regardless

11. Schnedorf, J. G.; Bradley, W. B., and Ivy, A. C.: Effect of Acetylsalicylic Acid upon Gastric Activity and the Modifying Action of Calcium Gluconate and Sodium Bicarbonate, Am. J. Digest. Dis. & Nutrition **3**:239, 1936. Reid and Ivy.[9]

of this died within a week, it is concluded that death after administration of cinchophen is due to some vital function of the liver unrelated to the synthesis and excretion of cholic acid or to some general toxic effect not confined to the liver.

Since synthesis and secretion of cholic acid occur in the fasting animal, since cholic acid introduced into the intestine was not secreted in the bile during various hourly periods of cinchophen medication in animals that were susceptible to the drug and since secretion of cholic acid may be completely suppressed temporarily without anorexia or other signs of gastrointestinal upset, it is concluded that the suppression of synthesis and secretion of cholic acid is due chiefly to the effect of the drug on the liver and not to its effect on the gastrointestinal tract. However, in the absence of an analysis of the bile for cholic acid, anorexia is the first and most reliable indication of sufficient damage to the liver to cause a failure of synthesis and secretion of cholic acid.

On the basis of the criterion of depression of secretion of cholic acid, susceptibility to the drug varies in the same and in different animals. This variation observed in a selected group of animals with biliary fistulas in this laboratory was more fully discussed in a previous paper.[12]

12. Annegers, J. H.; Snapp, F. E.; Atkinson, A. J., and Ivy, A. C.: Variations in Susceptibility to Cinchophen as Observed in Animals with Bile Fistulas, J. Lab. & Clin. Med. **28**:828, 1943.

THE MORGAGNI-STEWART-MOREL SYNDROME

REPORT OF A CASE WITH PNEUMOENCEPHALOGRAPHIC FINDINGS *

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PHILADELPHIA

The symptom complex of hyperostosis frontalis interna, or its variants described by Sherwood Moore,[1] with associated endocrine and neuropsychiatric manifestations, had stimulated a degree of interest, as evidenced by the increasing literature on the subject, to warrant the report of cases which may throw more light on the etiologic background of this interesting condition. The triad of hyperostosis frontalis interna, obesity and virilism had been described originally by Morgagni [2] in 1765. Much later (1928) the appearance of a more careful study, by Stewart,[3] in which he described the autopsy observations and added the clinical feature of a psychosis to the syndrome, and the first description of the syndrome as observed in a living person, by Morel [4] in 1930, brought the group picture of calvarial hyperostosis and endocrine, metabolic and neuropsychiatric manifestations into clearer relief as an entity. Moore's elaborate work in reexamining roentgenograms of numerous human skulls revealed that among 6,650 specimens four types of calvarial hyperostosis could be distinguished, their frequency in order of appearance being hyperostosis frontalis interna 1.44 per cent, nebula frontalis 1.14 per cent, hyperostosis calvariae diffusa 0.6 per cent and hyperostosis frontoparietalis 0.3 per cent. He defined a symptom complex which later he termed "metabolic craniopathy." [1c] A complete review of the literature and of the hypotheses regarding the causation and the descriptions of the pathologic changes are not the purpose of this paper and may be consulted in the excellent reviews by Knies and Le Fever,[5] Perkins and Biglan [6] and Andrews.[7] The entire syndrome has been broadened to include both the original concept of Morgagni and those of Stewart and Morel and the signs and symptoms described by subsequent authors. In the main, the syndrome consists of the following elements: one of the types of calvarial hyperostosis as described by Moore; endocrine and metabolic disturbances, such as obesity, virilism and menstrual disorders in female patients and gonadal deficiency in male patients; hypertension, and neuropsychiatric manifestations, such as headaches, cranial nerve defects (disturbance in olfaction, seventh nerve palsy, diplopia, amblyopia), fatigability, muscular weakness, narcolepsy, convulsive seizures, incoordination, dizziness, staggering gait, attacks of sweating, disturbances of speech, mental dulness, defects of memory, changes in personality, irritability, mental deterioration and, terminally, dementia. It is not essential, however, that all of these manifestations, with the exception of the pathognomonic roentgen finding of hyperostosis interna, he found in an individual case. Briefly, the cause, although by no means definitely established, appears to be of both metabolic and endocrine origin,[8] concerned

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|| From the University of Pennsylvania, Graduate School of Medicine.

1. Moore, S.: (*a*) Hyperostosis Frontalis Interna, Surg., Gynec. & Obst. **61**:345-362, 1935; (*b*) Calvarial Hyperostosis and the Accompanying Symptom Complex, Arch. Neurol. & Psychiat. **35**:975-981 (May) 1936; (*c*) Metabolic Craniopathy, Am. J. Roentgenol. **35**:30-39, 1936.

2. Morgagni, J. B.: De sedibus et causis morborum per anatomen indogatis libri quinque, ed. 2, Padua, sumpt. Pemondini, 1765, book 2, epistle 27.

3. Stewart, R. M.: Localized Cranial Hyperostosis in the Insane, J. Neurol. & Psychopath. **8**:321-331, 1928.

4. Morel, F.: L'hyperostose frontale interne: Syndrome de l'hyperostose frontale interne avec adipose et troubles cérébraux, Paris, Gaston Doin & Cie, 1930.

5. Knies, P. T., and Le Fever, H. E.: Metabolic Craniopathy: Hyperostosis Frontalis Interna, Ann. Int. Med. **14**:1858-1888, 1941.

6. Perkins, O. C., and Biglan, A. M.: Hyperostosis Frontalis Interna: A Review of the Literature, Psychiatric Quart. **12**:340-350, 1938.

7. Andrews, C. T.: Hyperostosis Frontalis Interna, Brit. M. J. **2**:185-187, 1942.

8. (*a*) Mortimer, H.: Influence of Anterior Pituitary on Cranial Form and Structure, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:222-238, 1938; (*b*) in discussion on Carr,[8d] p. 986 (*c*) Mortimer, H.; Levene, G., and Rowe, A. W.: Cranial Dysplasias of Pituitary Origin, Radiology **29**:135-157 and 279-290, 1937. (*d*) Carr, A. D.: Neuropsychiatric Syndromes Associated with Hyperostosis Frontalis Interna, Arch. Neurol. & Psychiat. **35**:982-989 (May) 1936. (*e*) Henschen, F.: Hyperostosis verrucosa frontalis interna und deren Bedeutung, Acta path. et microbiol. Scandinav., 1936, supp. 26, pp. 95-97; (*f*) Le "syndrome de Morgagni" (hyperostose frontale interne, virilisme, adipose), Ann. d'anat. path. **13**:943-960, 1936; (*g*)

(Footnotes continued on next page)

chiefly with fat and calcium derangement and dysfunction of the anterior lobe of the pituitary and the parathyroid, thyroid and adrenal glands. It is the consensus among most observers that this syndrome occurs almost exclusively in the female, Moore [1b] reporting a 98 per cent incidence, and is seen mainly in late adult life.

It will be seen from the symptoms enumerated and will be illustrated in the following case report that this syndrome may be readily confused with other endocrine or neuropsychiatric disorders, especially psychoneuroses, dementia paralytica, multiple sclerosis and tumor of the brain.[9] It is important, therefore, not to fall into the error either of minimizing the significance of the symptoms, thereby escaping the diagnosis, or of treating the patient "for something which he does not have." [1b]

The following case is reported to illustrate failure to recognize the condition over a period of many years because of the slow, progressive and apparently innocuous nature of the disease, which was euphemistically dismissed as a harmless psychoneurosis, and because of the pneumoencephalographic findings, which may yield some information affording a better understanding of the neuropsychiatric aspects of the syndrome. Only one report of pneumoencephalographic findings has appeared thus far in the literature; Knies and Le Fever [5] reported plastic arachnoiditis in one case (case 20) and dilatation of the anterior horns of the lateral ventricles in another (case 24).

REPORT OF CASE

A. G., a married woman aged 39, was admitted to the neurologic service of the Doctors Hospital, on Nov. 20, 1942, giving as chief complaints headaches and attacks of drowsiness accompanied with convulsive seizures. Her family physician had made the diagnosis of a psychoneurosis.

Both parents were dead; the father died in an accident at 36 years of age; her mother died of pneumonia at 59 years of age. Three siblings were living and well. There was no history of tuberculosis, cancer, diabetes, cardiorenal disease, epilepsy or mental disease in the immediate or collateral members of the family. At the age of 8 years she had a minor injury of the head. The menses began when she was 11 years old and occurred at irregular intervals. Since the birth of a son, her only child, 12 years prior to her admission to the hospital, her periods had been regular but the flow scanty.

Her presenting complaints, drowsiness and "shaking spells," had occurred frequently during the three months prior to admission. These spells usually came on about one hour or so after meals, often manifesting themselves in an abortive form by discomfort and inability to concentrate. Although vague about the time of inception of her present illness, she believed it began about ten years previously, with buzzing in the head. Six years previously she experienced "violent blood rushes to the head," which on the following day were succeeded by headache and profuse sweating. This endured for one year. Drowsiness made its appearance about five years before her admission, and accompanying this was an impairment of memory. Moreover, visual disturbances, consisting of "haze" over her eyes and a sensation of "sand in her eyes," together with double vision, came on about this time. The double vision, although still present at times, had receded considerably. She had consulted numerous ophthalmologists and finally, by a process of self-taught "ocular exercise," had found improvement. During the past year, having been employed as a telegrapher, she had noted that she would omit syllables or whole words and occasionally transpose words. For the past few years she had slept poorly, and recently she had experienced a sensation as though some one were under her bed pulling the bedclothes off and at times pushing her feet up. For three or four years past she had had bouts of "grogginess" and staggering gait, often being taken for a "drunk." Recently, during these periods of uncertain gait she had suffered from clumsiness with her hands so that she often dropped objects. Moreover, she had been told that at such times she took on a peculiar expression with a livid color to the skin and that her eyelids drooped. The "shaking spells," although present for a longer time, had occurred at frequent intervals during the past six months. These appeared at any time during the day or night, and she did not recall the duration of each seizure. Headache had been present for six months. The pain involved mainly the left side, but occasionally it was initiated over the forehead and involved the right side as well. She had not been able to work during the past six months because of the many symptoms besetting her. The numerous physicians whom she had consulted, usually put her off with the statement "go home and forget about it; you're just trying to get sympathy for yourself."

The patient was a fairly well developed woman. During the period of observation in the hospital she was given to swings of mood, at some times being euphoric and at others moody and depressed. During her elated phases she was extremely garrulous and discussed her many symptoms with a degree of relish. Occasionally she would stop abruptly while speaking and state that she had completely forgotten what she had intended saying. She was abrupt in manner and suspicious and believed that her period of observation in the hospital constituted making her a "guinea-pig." She was properly oriented for time, place and person, but at times, after giving correct replies, she would say that she did not know who she was or where she was. Memory for recent events was not impaired, but she was evasive when being tested for remote events. There was some impairment of immediate recall. She showed no hallucinatory or delusional trends while in the hos-

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Morgagni Syndrome, Hygiea **48**:65-85, 1936; (*h*) Morgagnis Syndrom: Hyperostosis frontalis interna, Virilismus, Obesitas, in Aschoff, L.; Culen, W.; Koch, W., and Schürmann, P.: Veröffentlichungen aus der Konstitutions- und Wehrpathologie, 1937, Berlin, Gustav Fischer, vol. 9, pp. 1-82. (*i*) Grieg, D. M.: On Intracranial Osteophytes, Edinburgh M. J. **35**:165-191 and 237-260, 1928. (*j*) Dressier, L.: Ueber die Hyperostosen des Stirnbeins, Beitr. z. path. Anat. u. z. allg. Path. **78**:332-363, 1927.

9. Knies and Le Fever.[5] Carr.[8d] Schwab, S. I., in discussion on Carr,[8d] p. 985.

pital. Throughout her stay of twenty-two days she continuously questioned the need for studies. She would remain in bed for several days in a surly, negativistic mood, followed by a period of considerable activity during which she would walk up and down the hospital corridors.

Fig. 1.—Note the generalized thickening and increased density of the skull (which prevented proper penetration of the x-rays) with marked hyperostosis frontoparietalis interna.

The contour of the skull was normal. There was no defect in olfaction. Vision was intact, and the fields were full. The ophthalmoscopic examination showed a general hyperemia of the disks and retinas. The vessels were full, especially the veins, which were broader than normal. The left eye was larger and somewhat proptosed, producing the appearance of a left external strabismus. The pupils were round, regular and equal and responded promptly to light and in accommodation. The extraocular movements were well performed in all directions. Diplopia and nystagmus could not be brought out. There was a mild facial weakness on the left, central in type. The remaining cranial nerves were normal. Muscular weakness was present in a mild form. The biceps and triceps reflexes were very prompt, and a radial periosteal reflex was present bilaterally. A suggestive Hoffman sign was present in the left hand. The abdominal reflexes were absent. The knee jerks and ankle jerks were exaggerated, but

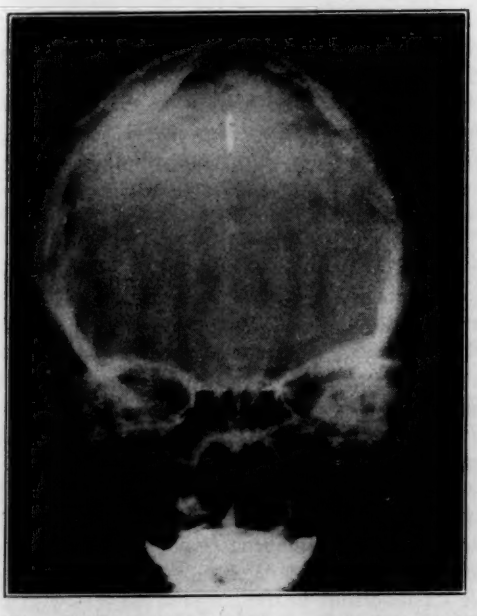

Fig. 2.—Posteroanterior view. The hyperostosis interna is marked just lateral to the vertex. The calcification in the falx measures 4 mm. by 2 cm.

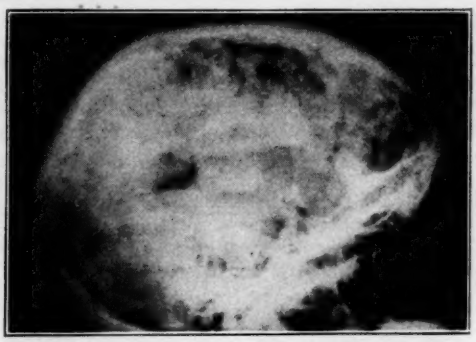

Fig. 3.—Pneumoencephalogram, lateral view. The thickness of the skull and the frontoparietal hyperostosis interna are more apparent here. Observe the extreme atrophy of the frontal and parietal lobes, the dilatation of the lateral ventricles and the irregular outline of the roof of the lateral ventricles.

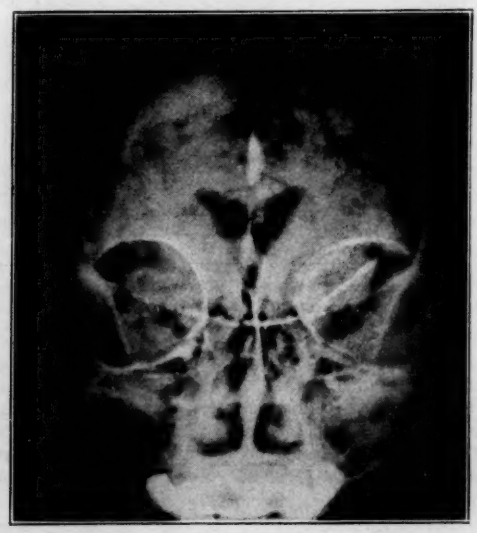

Fig. 4.—Pneumoencephalogram, anteroposterior view, showing cortical atrophy, pronounced atrophy of the islands of Reil, moderate enlargement of the lateral ventricles and calcification of the falx just above the corpus callosum.

pathologic reflexes were not obtained. Coordination was unimpaired. The Romberg maneuver, station and gait were normal. Sensation was intact throughout in all modalities. The chest, abdomen and limbs showed no abnormalities. The temperature varied from normal to 99.4 F. The blood pressure was 118 systolic and 90 diastolic and the pulse rate 72. The third day after admission she had an "attack" described by the nurse as a "wave of tremors and spasms, rigid body, left eye turned outward, unable to talk and unable to move."

Roentgenograms of the skull showed an increased thickness and density of bone throughout the frontal, parietal and occipital regions. In addition, there were irregular hyperostoses of the inner table of the frontal and parietal bones. The sella turcica was small, and the clinoid processes were almost completely bridged. Calcification of the falx, measuring 4 mm. by 2 cm., was present (figs. 1 and 2).

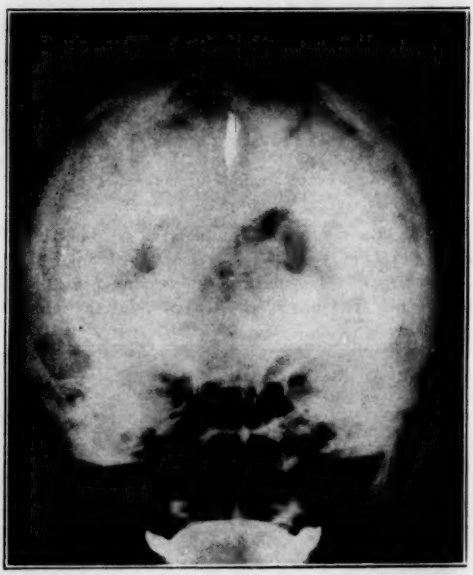

Fig. 5.—Pneumoencephalogram, posteroanterior view, showing enlarged, asymmetric lateral ventricles and the hyperostosis in relief.

In view of the roentgen findings of a thickened calvarium with frontoparietal hyperostosis interna associated with the neuropsychiatric phenomena, the diagnosis of Morgagni-Stewart-Morel syndrome was made. The similarity of many of the behavioral peculiarities, personality changes and mental symptoms to those of dementia paralytica prompted the performance of pneumoencephalography in the hope of finding some explanation in terms of intra-vitam cerebral changes.

Pneumoencephalography was performed on Nov. 27, 1942. Spinal puncture, with the patient in the recumbent position, showed an initial pressure of 74 mm. of cerebrospinal fluid. After 158 cc. of cerebrospinal fluid had been removed and 150 cc. of air injected in small amounts, there was still a free flow of fluid. The pneumoencephalograms showed pronounced cortical atrophy over the frontal and parietal lobes, atrophy of the islands of Reil and moderately advanced internal hydrocephalus, with asymmetry and irregularity of the lateral ventricles (figs. 3, 4 and 5). Laboratory studies showed: normal blood cell count; normal results of urinalysis; normal cerebrospinal fluid; normal serologic reactions of blood and cerebrospinal fluid; blood calcium 11.2 mg. per hundred cubic centimeters, blood phosphorus 2.5 mg. and blood cholesterol 300 mg.; basal metabolic rate, —23, —10 and +2; sugar tolerance, during fasting 70 mg. at one-half hour 145 mg. and at one hour 165 mg. per hundred cubic centimeters; urinary creatinine, 549, 497 and 787 mg. per liter on successive days; creatine + creatinine, 609, 1,224 and 860 mg. per liter.

During the last ten days in the hospital she received some form of gelatin with each meal and an amino acid preparation. She believed there was slight improvement in her headache and an increase in strength. This report may have been unreliable, because after being discharged she refused treatment and expressed paranoid ideas.

COMMENT

Cases of the composite syndrome of hyperostosis frontalis interna with accompanying neuropsychiatric manifestations associated with cerebral atrophy pose a number of interesting questions: Are the mental symptoms related to the cerebral atrophy? Is the cerebral atrophy a secondary process caused by the impingement of the hyperostotic osteophytes? Is the cerebral atrophy primary and the hyperostosis a compensatory process? Are the bony and cerebral changes due to separate and unrelated mechanisms, or are they individual reactions of the tissues to essentially the same constitutional disturbances in the metabolic and endocrine spheres or perhaps to some as yet unidentified factor? Moore,[1] in describing the bony changes of what he termed "metabolic craniopathy," stated that "the skull does not increase in size—this fact is significant for the reason that the increased volume of the bone under these circumstances has to be accommodated at the expense of the capacity of the cranial cavity." This implies that the brain is involved either by direct pressure or by a disturbance secondary to diminished volume of blood or cerebrospinal fluid and indirectly implies that such changes could be responsible for the neuropsychiatric aspects of this syndrome. The similarity of the atrophy described in the case presented here to that seen in pneumoencephalograms in cases of dementia paralytica[10] would indicate that there is a relationship of the atrophic changes with the mental symptoms. Moreover, the pneumoencephalographic and autopsy evidence of cerebral atrophy in such conditions as presenile sclerosis (Alzheimer's disease), Pick's disease and pro-

10. Moore, M. T.; Nathan, D.; Elliott, A. R., and Laubach, C.: Encephalographic Studies in Mental Disease, Am. J. Psychiat. **92**:43-67, 1935.

gressive subcortical encephalopathy (Schilder's disease), which present neuropsychiatric symptoms, again would substantiate the relationship between the atrophy and the nervous and mental symptoms. There is much disagreement regarding the question as to which comes first, that is, whether the cranial hyperostosis is followed by the cerebral degeneration or whether the process is the reverse. Morel [4] originally believed that the hyperostosis interna damaged the underlying brain directly, but later [11] he retracted this view and concurred with Grieg,[8i] who expressed the opinion that the intracranial osteophytes did not of and by themselves produce cerebral damage or bring on mental symptoms. Others have maintained that the pressure exerted by the hyperostosis results in cortical degeneration, whereas Henschen,[12] Schneider [13] and Stewart [14] have presented convincing data that the pressure exerted by the frontal hyperostosis does not per se produce the neuropsychiatric signs and symptoms. The encephalograms (figs. 3, 4 and 5) show that the areas of cortical atrophy are not in direct contact with the hyperostoses at all points but that fluid-filled spaces exist between the inner table of the skull and the brain. This observation would also preclude the contention that the hyperostosis fills in the "dead space" as a compensatory mechanism. Stewart [14] showed this conclusively in a report on a 68 year old woman presenting an advanced form of hyperostosis frontalis interna, stating:

> The brain showed a massive lobar softening of three years' duration, limited to the right cerebral hemisphere, the other hemisphere showing only a minor degree of senile atrophy. The opinion is expressed that this crossed relationship between the gross atrophy of the right cerebral hemisphere and the thicker left half of the pars frontalis lends no support for the view that in hyperostosis frontalis interna, reduction of the volume of the brain stimulates the deposit of new bone.

Roth [15] would make it appear that the cranial bony changes and the neuropsychiatric manifestations are of separate origin. He stated that "neurologic and mental sequelae, as a consequence of the presence of the hyperostoses, appear to be quite infrequent"—this despite the fact that all of his 8 patients presented either psychiatric or neurologic conditions—and concluded that "the neuropsychiatric signs and symptoms were the result of other factors, such as cerebral arteriosclerosis, hypertension, etc." It must be borne in mind that the mental symptoms may antedate by as much as ten or twenty years [5] the final establishment of the diagnosis by the roentgenogram. The patient reported on here, aged 39, showed no evidence of arteriosclerosis, and blood pressure readings were low. Moreover, some of her symptoms were of ten years' duration. Knies and Le Fever [6] have reported frontal hyperostosis in a 7 year old boy, son of a 41 year old woman who had the symptom complex of hyperostosis frontalis interna, with endocrine and neuropsychiatric disturbances.

Hemphill and Stengel [16] reported the histopathologic observations in the case of a 65 year old patient presenting the syndrome of frontal hyperostosis: The brain exhibited a diffuse and focal loss of ganglion cells of the third and fifth, and to a lesser degree of the sixth, cortical layers in the frontal and parietal lobes. The cerebral blood vessels showed no marked changes. Pathologic changes were found in the anterior lobe of the pituitary, parathyroid, thyroid and adrenal glands. The encephalographic examination in the case herein reported revealed a degree of atrophy which histologically would be comparable to that described in the above case.

The patient reported on here had menstrual irregularities and imbalance of the vegetative nervous system. The laboratory data, showing the disparity of the abnormal calcium-phosphorus ratio, the high blood cholesterol level, low basal metabolic rate and disturbed sugar tolerance, are indicative of both metabolic and endocrine disturbances. Mortimer [17] and his associates have shown the relationship existing between calcium and fat metabolism and the function of the anterior lobe of the hypophysis and have expressed the belief that the Morgagni-Stewart-Morel syndrome results from endocrine dysfunction, mainly of pituitary origin. Others [8] also have offered an explanation for the varied symptoms on an endocrine basis. It appears, therefore, that this syndrome is in fact a constitutional disorder manifesting itself in a peculiar localized involvement of the cranial bones and a

11. Morel, F.: L'hyperostose frontale interne, Schweiz. med. Wchnschr. **67**:1235-1237, 1937.

12. Henschen (footnote 8 *e*, *f*, *g* and *h*).

13. Schneider, E.: Zur Kenntnis der Schädelosteome und der Hyperostosis frontalis, Med. Klin. **32**:487-490, 1936.

14. Stewart, R. M.: Hyperostosis Frontalis Interna: Its Relationship to Cerebral Atrophy, J. Ment. Sc. **87**: 600-607, 1941.

15. Roth, N.: The Syndrome of Frontal Internal Hyperostosis, Am. J. Psychiat. **98**:63-69, 1941.

16. Hemphill, R. E., and Stengel, E.: Morgagni's Syndrome: A Clinical and Pathological Study, J. Ment. Sc. **86**:341-365, 1940.

17. Mortimer.[8a, b] Mortimer, Levene and Rowe.[8c]

biochemical and morphologic disturbance in the brain.

In view of the fact that the Morgagni-Stewart-Morel syndrome often occurs in incomplete patterns, it would not be too hazardous at this time to venture the view that the cerebral changes occur, at a slow and irregular rate to be sure, *pari passu* with the metabolic craniopathy and reflect a reaction of the individual tissues to an altered metabolic state. When the craniopathy and endocrine manifestations predominate and no overt psychoneurosis or psychosis exists, then the Morgagni appellation is given; however, if in addition neuropsychiatric disorders appear, the Stewart-Morel designation is attached.

SUMMARY

A woman presented the syndrome of calvarial hyperostosis with metabolic, endocrine and neuropsychiatric disturbances (Morgagni-Stewart-Morel syndrome). Pneumoencephalographic studies showed evidence of cerebral degeneration in the form of frontoparietal cortical atrophy, atrophy of the islands of Reil, asymmetry of the lateral ventricles and moderate internal hydrocephalus.

1813 Delancey Street.

EFFECTIVENESS OF VARIOUS SULFONAMIDE DRUGS AND NEOARSPHENAMINE AGAINST PNEUMOCOCCI IN BONE MARROW CULTURES

A COMPARATIVE STUDY

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In previous publications it has been shown that sulfanilamide is more effective against pneumococci in bone marrow cultures than antiserum is, that sulfanilamide plus antiserum is much more effective than either alone,[1] that sulfapyridine alone is much more effective than sulfanilamide plus antiserum and that sulfapyridine plus antiserum is definitely more effective than sulfapyridine alone.[2] Sulfathiazole has been shown to be much more effective against staphylococcic infections than sulfapyridine.[3] The relative effectiveness of several sulfonamide drugs against pneumococci is presented in the present study.

The marrow culture method has proved to be effective for controlled, quantitative measurement of the action of therapeutic agents on bacteria in the presence of living human cells.[4]

EXPERIMENTAL STUDY

About 50 cc. of a culture which contained about 100,000,000 living human nucleated marrow cells in a medium which consisted of 35 per cent human cord serum obtained from the fetal side of the placenta and 65 per cent balanced salt solution [5] was placed in a 50 cc. vaccine vial and inoculated with recently isolated virulent strains of various types of pneumococci from the

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Dr. Bullowa wrote this paper from marrow culture data submitted to him by Dr. Osgood. Because of a protracted illness, followed by death on Nov. 9, 1943, he was unable to include the clinical data as planned.

These studies received financial support from the Dazian Fund, the Littauer Pneumonia Research Fund, the Metropolitan Life Insurance Company, Mr. Bernard M. Baruch, Mr. Bernard M. Baruch Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

From the Medical Service of Harlem Hospital and the Department of Hospitals of the City of New York, Oswald LaRotunda, Director; from the Department of Medicine and the Division of Experimental Medicine, University of Oregon Medical School, and from the Littauer Pneumonia Research Fund of New York University College of Medicine.

1. Osgood, E. E.: Culture of Human Marrow: A Comparative Study of the Effects of Sulfanilamide and Antipneumococcus Serum on the Course of Experimental Pneumococcic Infections, Arch. Int. Med. **62**: 181-198 (Aug.) 1938.

2. Bullowa, J. G. M.; Osgood, E. E.; Bukantz, S. C., and Brownlee, I. E.: The Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures: Results in Four Hundred and Thirty-Seven Pneumococcic Pneumonia Patients Rotated for Treatment, Am. J. M. Sc. **199**:364-380 (March) 1940.

3. (*a*) Osgood, E. E.: Effectiveness of Neoarsphenamine, Sulfanilamide and Sulfapyridine in Marrow Cultures Infected with Staphylococci and Alpha Streptococci, Proc. Soc. Exper. Biol. & Med. **42**:795-797 (Dec.) 1939. (*b*) Osgood, E. E.; Joski, J., and Brownlee, I. E.: The Superiority of Neoarsphenamine and Sulfathiazole in the Therapy of Staphylococcus Aureus Infections in Marrow Cultures, Surg., Gynec. & Obst. **71**:445-450 (Oct.) 1940.

4. Osgood, E. E.: (*a*) Marrow Cultures, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, pp. 219-241; (*b*) Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110**:349-356 (Jan. 29) 1938; (*c*) Culture of Human Marrow: Studies of the Relative Effectiveness of Neoarsphenamine, Mapharsen, Sulfanilamide, Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole on Infections with Streptococcus Viridans (Alpha Hemolytic Streptococcus), Am. J. M. Sc. **200**:596-603 (Nov.) 1940.

5. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Details of a Simple Method, J. A. M. A. **108**:1793-1796 (May) 1937.

pneumonia service of Harlem Hospital, New York. After thorough mixing, pour plate colony counts were made, and equal volumes of culture were placed in each of six to eight 30 cc. vaccine vials. To each of these except one, which was left as a control, the desired concentration of one of the sulfonamide compounds to be tested was added. The cultures were then placed in the incubator. At intervals samples were removed from each vial, and pour plate colony counts and stained smears were made. This technic insures that the cultures from one experiment are identical in every respect except for the drugs purposely introduced. Examples of the types of results obtained in individual experiments are shown in tables 1 to 4. The stained smears from these experiments show the appearance which would be expected from the colony counts, as illustrated in figures 4 to 9 in an article by Schmith.[5a]

TABLE 1.—*Experiment with Type VII Pneumococci* *

	Hours			
	0	6	25	49
Control	180	24,500	270,000,000	
Sulfapyridine 1:20,000	180	750?	.....	00
Sulfathiazole 1:20,000	180	250?	.....	00
Sulfamethylthiazole 1:20,000	180	150?	.....	1
Sulfaphenylthiazole 1:20,000	180	50,000	300,000,000	

* The figures represent colony counts.

Sulfapyridine and sulfathiazole were extremely effective against pneumococci. In order to show a difference, comparatively large inoculations were used and a 1:20,000 concentration, which corresponds to 5 mg. of the drugs per hundred cubic centimeters. Even under these conditions, in the majority of the experiments both sulfapyridine and sulfathiazole led to sterility after twenty-four to seventy-two hours, as is shown in table 1. They therefore appeared to be equally effective. (Against some strains, however, sulfapyridine was more effective than sulfathiazole [table 2], and against other strains sulfathiazole was more effective than sulfapyridine [table 3].) In the experiment summarized in table 1 sulfaphenylthiazole was completely ineffective, as was sodium sulfanilyl sulfanilate in the experiments reported in tables 2 and 3. Sulfamethylthiazole according to tables 2 and 3 was extremely effective, but it was definitely less effective as a rule than sulfapyridine and sulfathiazole, although there were occasional exceptions. In table 4 sulfapyridine and sulfathiazole are shown to have been equally effective, sulfamethylthiazole of some value and sulfaphenylthiazole totally ineffective.

TABLE 2.—*Experiment with Type V Pneumococci* *

	Hours			
	0	27	30	54
Control	390	100,000,000	.....	.....
Sulfapyridine 1:20,000	390	.....	50	100,000
Sulfathiazole 1:20,000	390	.....	4,000	30,000,000
Sulfamethylthiazole 1:20,000	390	.....	30,000,000	250,000
Sodium sulfanilyl sulfanilate 1:20,000	390	100,000,000		

* The figures represent colony counts.

Table 5 summarizes the results of the experiments. As we have previously reported,[6] different strains of the same type of pneumococcus showed marked differences in susceptibility to these drugs. The strain of type IV investigated in these experiments was relatively resistant to all of the drugs investigated, although in other experiments strains of type IV have been found which were highly susceptible to the action of sulfapyridine. It is noteworthy that in 11 of the 22 experiments sulfapyridine and sulfathiazole led to sterility and thus were equally effective. Sulfamethylthiazole led to sterility in 7 of the 20 experiments in which it was used. In 2 of the experiments with pneumococci of type VIII all three drugs were equally, but only slightly, effective. This makes a total of 4 of the

TABLE 3.—*Experiment with Type VII Pneumococci* *

	Hours			
	0	27		54
Control	280	100,000,000		
Sulfapyridine 1:20,000	280	.....	9,800	9,000
Sulfathiazole 1:20,000	280	.....	35	107
Sulfamethylthiazole 1:20,000	280	.....	.....	161,000
Sodium sulfanilyl sulfanilate 1:20,000	280	100,000,000		

* The figures represent colony counts.

TABLE 4.—*Experiment with Type VIII Pneumococci* *

	Hours			
	0	6	25	48
Control	820	17,800	100,000,000	
Sulfapyridine 1:20,000	820	400?	50	0
Sulfathiazole 1:20,000	820	100?	50	0
Sulfamethylthiazole 1:20,000	820	200?	50	75?
Sulfaphenylthiazole 1:20,000	820	300?	250,000,000	

* The figures represent colony counts.

5a. Schmith, K.: Experimental Studies on the Effect of Sulfapyridine on Pneumococci and Gonococci, Copenhagen, Arnold Busck, 1941.

6. Bullowa, Osgood, Bukantz and Brownlee.[2] Osgood.[4]

22 experiments in which sulfapyridine and sulfathiazole were equally effective and of 10 of the 20 in which sulfamethylthiazole was as effective as sulfapyridine and sulfathiazole. In 1 experiment sulfapyridine was definitely superior to sulfathiazole, and in 7 experiments sulfathiazole was superior to sulfapyridine. Neoarsphenamine was totally ineffective against all strains of pneumococci tested; hence data on tests with it are omitted from the tables.

From these observations it may be concluded that there is no reason ever to employ sulfamethylthiazole in the treatment of pneumonia, because both sulfapyridine and sulfathiazole offer more promise and are not as toxic. From the standpoint of absolute effectiveness under these conditions there is no choice between sulfapyridine and sulfathiazole.

TABLE 5.—*Comparative Effectiveness of Drugs Against Pneumococci* *

Type	Strain	Inoculation	Sulfapyridine	Sulfathiazole	Sulfamethylthiazole
I	A	2	6	6	6
I	B	0	0	0	0
II	..	3	6	3	5
III	..	2	5	2	4
IV	A	3	8	8	8
IV	A	3	8	8	8
V	A	2	0	0	0
V	A	2	5	7	5
VII	A	1	0	0	8
VII	A	2	0	0	0
VII	A	3	5	2	3
VII	B	2	4	0	2
VII	B	2	3	1	5
VIII	A	2	0	0	0
VIII	A	2	0	0	0
VIII	B	3	8	5	6
VIII	B	3	7	5	7
XII	A	1	0	0	0
XII	A	3	0	0	0
XXV	A	2	0	0	
XXV	A	2	0	0	

* The figures represent the logarithm of the final colony count.

This series of experiments employing a single concentration of the drugs was completed before sulfadiazine and sulfathiazoline (2-sulfanilyl-3,5-dihydrothiazole) were available. Later, observations were made employing several dilutions of each drug and several sizes of inoculum as well as different strains, because these are the factors which influence effectiveness. These results are shown in table 6. The observations of Schmith [5a] that susceptibility of organisms may be described in terms of number of organisms and concentration of sulfapyridine to which they are vulnerable is supported by these results. A discussion of table 6 follows:

Inoculation of 100 Organisms per Cubic Centimeter or Less.—With 20 organisms per cubic centimeter of a type IV strain (J. H.) of pneumococci, sulfathiazole was superior to sulfadiazine. The culture was sterilized with 10 mg. of sulfadiazine per hundred cubic centimeters but not with 5 mg., whereas sulfathiazole was effective with 5 mg. per hundred cubic centimeters. With 24 organisms per cubic centimeter of a type VII strain (G. S.) of pneumococci, 5 mg. of sulfathiazole per hundred cubic centimeters was effective, as was 20 mg. of sulfadiazine per hundred cubic centimeters (the only concentration used). With 10 mg. per hundred cubic centimeters sterilization by sulfathiazole occurred, though it was delayed. With an inoculum of 100 organisms per cubic centimeter of a type XII strain (R. J.) of pneumococci, 5 mg. of sulfathiazole per hundred cubic centimeters, 20 mg. of sulfadiazine and 10 mg. of sulfathiazoline were effective. Sulfanilamide was ineffective.

Inoculation of More than 100 Organisms per Cubic Centimeter and Less than 200.—Sulfathiazole was superior to sulfadiazine with an inoculum of 141 organisms per cubic centimeter of a type VII strain (G. S.) of pneumococci. Sulfadiazine sterilized in a concentration of 20 mg. per hundred cubic centimeters but not in a concentration of 10 mg. per hundred cubic centimeters, whereas 5 mg. per hundred cubic centimeters of sulfathiazole produced sterility. With 128 organisms per cubic centimeter of a type IV strain (J. H.) of pneumococci, 5 mg. per hundred cubic centimeters of sulfathiazole was as effective as 10 mg. of sulfadiazine.

Inoculation of 200 to 500 Organisms per Cubic Centimeter.—With 276 organisms per cubic centimeter of a type I strain (M. Ber.) of pneumococci, 20 mg. of sulfadiazine per hundred cubic centimeters was slightly better than 5 mg. of sulfathiazole per hundred cubic centimeters, but neither resulted in sterility. With 350 organisms per cubic centimeter of a type I strain (M. Ben.) of pneumococci, 5 mg. of sulfathiazole per hundred cubic centimeters was better than 20 mg. of sulfadiazine per hundred cubic centimeters in effecting sterility. With 330 organisms per cubic centimeter of a type I strain (M. Ben.) of pneumococci, 5 mg. of sulfathiazole per hundred cubic centimeters was superior to 20 mg. of sulfadiazine in effecting sterility. With 220 organisms of a type IV strain (B. G.) of pneumococci sterilization was not accomplished by 5 mg. of sulfathiazole per hundred cubic centimeters or by 10 mg. of sulfadiazine. With 458 organisms per cubic centimeter of a type VIII strain (L. T.) of pneumococci, neither sulfathiazole nor sulfadiazine in a concentration of 5 mg. per hundred cubic centimeters resulted in sterility.

TABLE 6.—*Experiments in Which Different Concentrations of Drugs, Sizes of Inoculums and Strains Were Used*

Case	Name of Patient	Pneumococcus Type	Drug	Concentration, Mg./100 Cc.	Initial Inoculum	Logarithm of Bacterial Population: Hours After Inoculations						
						0	16-20	20-24	24-40	40-49	49-78	78-143
1	M. B.	I	.....	Control	276	2.44	8.3	....	....	....	....	....
			Sulfathiazole	5	...	2.44	5.98	6.75	....	8.3		
			Sulfadiazine	5	...	2.44	8.3					
			Sulfadiazine	20	...	2.44	4.90	5.59	....	6.72		
2	M. B.	I	.....	Control	330	2.52	7.22	....	8.3	....	....	....
			Sulfadiazine	5	...	2.52	4.63	....	....	6.90	8.3	
			Sulfadiazine	10	...	2.52	3.12	....	....	3.79	2.99	
			Sulfadiazine	20	...	2.52	3.02	....	....	2.78	2.57	
			Sulfathiazole	5	...	2.52	2.60	....	....	2.84		
3	C. T.	III	.....	Control	670	3.83	....	7.91	7.34	....	....	....
			Sulfadiazine	5	670	3.83	....	7.71	8.20	8.3		
			Sulfathiazole	10	670	3.83	....	4.05	4.20	4.08	5.74	
4	J. H.	IV	.....	Control	20	1.3	8.3	....	....	....	....	....
			Sulfadiazine	5	...	1.3	4.36	....	....	6.21		
			Sulfadiazine	10	...	1.3	2.0	....	....	0		
			Sulfadiazine	20	...	1.3	1.7	....	....	0		
			Sulfathiazole	5	...	1.3	1.7	....	....	0		
4	J. H.	IV	.....	Control	980	2.99	8.3	....	....	....	....	....
			Sulfadiazine	5	...	2.99	3.0	....	....	0		
			Sulfadiazine	10	...	2.99	2.0	....	....	0		
			Sulfadiazine	20	...	2.99	1.7	....	....	0		
			Sulfathiazole	5	...	2.99	1.7	....	....	0		
4	J. H.	IV	.....	Control	128	2.11	....	8.3	....	....	....	....
			Sulfathiazoline	5	...	2.11	....	....	0	0	0	
			Sulfathiazoline	10	...	2.11	....	....	0	0	0	
			Sulfanilamide	5	...	2.11	....	....	4.46	8.3	....	
			Sulfanilamide	10	...	2.11	....	....	4.40	5.1	7.85	
			Sulfadiazine	10	...	2.11	....	....	0	0	0	
			Sulfadiazine	20	...	2.11	....	....	0	0	0	
			Sulfathiazole	5	...	2.11	....	....	0	0	0	
5	B. G.	IV	.....	Control	220	2.34	8.3	....	....	....	....	....
			Sulfathiazoline	5	...	2.34	5.65	7.58				
			Sulfadiazine	5	...	2.34	7.87	8.3				
			Sulfadiazine	10	...	2.34	6.51	7.94				
6	G. S.	VII	.....	Control	24	1.38	....	....	....	....	....	....
			Sulfathiazoline	10	...	1.38	....	....	1.40	0	0	
			Sulfanilamide	10	...	1.38	....	....	4.96	8.3		
			Sulfadiazine	20	...	1.39	....	....	0	0	0	
			Sulfathiazole	5	...	1.39	....	....	0	0	0	
7	D. M.	VII	.....	Control	2,700	3.43	....	8.3	....	....	....	....
			Sulfadiazine	5	...	3.43	....	7.59	8.3			
			Sulfathiazole	5	...	3.43	....	4.25	4.70	8.3		
7	D. M.	VII	.....	Control	1,640	3.21	....	....	8.3	....	....	....
			Sulfadiazine	5	...	3.21	....	....	3.96	....	3.94	
			Sulfathiazole	5	...	3.21	....	....	3.04	....	0	
7	D. M.	VII	.....	Control	1,100	3.03	8.1	....	....	....	....	....
			Sulfadiazine	5	1,100	3.03	...	4.48	....	4.76	....	8.3
			Sulfathiazole	5	1,100	3.03	....	3.71	....	2.3	....	4.33
8	L. T.	VIII	.....	Control	458	2.66	....	7.79	....	....	....	....
			Sulfadiazine	5	458	2.66	....	7.04	7.55			
			Sulfathiazole	5	458	2.66	....	5.59	6.25	8.3		
9	R. J.	XII	.....	Control	100	2.0	....	....	....	....	....	....
			Sulfathiazoline	10	...	2.0	....	....	0	0	0	
			Sulfathiazole	5	...	2.0	....	....	0	0	0	
			Sulfanilamide	10	...	2.0	....	....	5.74	8.3		
			Sulfadiazine	20	...	2.0	....	....	0	0	0	

TABLE 7.—*Sources of Strains and Fates of Their Last Hosts.*

Patient's Initials	Type of Pneumococcus	Patient's Age	Blood Culture	Day of Disease Culture Taken for Study	Involvement	Day of Disease: Day Serum Started	Total Dose of Serum, Units	Drug Started	Total Grams Drug Given *	Total Days Drug Given	Highest Concentration	Day of Termination	Results
M. Ber.	I	50	.....	8th	RUL	9th	196,000 rabbit	....	.....	..	.....	14th	Recovered
M. Ben.	I	35	.....	2d	RUL, RLL	4th	75,000 rabbit	4th	10 NaSp.	2	3.6 on 5th	5th	Recovered
C. T.	III	32	Neg.	5th	LLL	4th	140,000 rabbit	4th	19 Sp.	4	4.7 on 6th	5th	Recovered
J. H.	IV	39	5—, 6, 9—	6th	RML, RLL	6th	617,500 rabbit	8th	25 Sd. 3 NaSp.	7 1	5.1 on 6th 6.1 on 8th 3.7 on 10th	10th (58 hr.)	Recovered
B. G.	IV	46	Neg.	....	Osteomyelitis of spine with sinus formation	....	.....	....	.....	..	.....	....	Recovered
G. S.	VII	28	7 8—	7th (spinal fluid) 7th (blood)	LLL	....	.....	7th	18 Sp.	6	3.7 on 8th 3.0 on 10th 3.5 on 12th	10th	Recovered
D. M.	VII	50	Neg.	7th	Bronchitis	....	.....	....	.....	..	3.3 on	....	Recovered
L. T.	VIII	59	Neg.	6th	RUL	....	.....	6th	13 Sd.	3	3.3 on 7th	7th	Recovered
R. J.	XII	10 mo.	Neg.	Ear and throat Jan. 15 †	RLL, RUL	8th	101,250 rabbit	9d	3.25 Sd. 1.65 Sd.	3 1	3.2 on 7th 6.7 on 8th 6.9 on 9th	7th	Recovered

* NaSp. indicates sodium sulfapyridine; Sp., sulfapyridine, and Sd., sulfadiazine.
† The history is too incomplete to fix the day of the disease. The patient was admitted to the hospital on December 18.

Inoculation of More than 500 Organisms per Cubic Centimeter.—With 670 organisms per cubic centimeter of a type III strain (C. T.) of pneumococci, 10 mg. of sulfathiazole per hundred cubic centimeters was more efficient than 5 mg. of sulfadiazine per hundred cubic centimeters, but sterility was not achieved. With 980 organisms per cubic centimeter of a type IV strain (J. H.) of pneumococci, sterility was achieved by sulfadiazine with 5, 10 and 20 mg. per hundred cubic centimeters and with sulfathiazole with 5 mg. per hundred cubic centimeters. When inoculums of 1,100 organisms per cubic centimeter of a type VII strain (D. M.) of pneumococci were employed, both sulfadiazine and sulfathiazole in a concentration of 5 mg. per hundred cubic centimeters failed to sterilize, though bacteriostasis was more prolonged with sulfathiazole. This was also the case with 2,700 organisms per cubic centimeter of the same strain.

SOURCES OF STRAINS OF ORGANISMS STUDIED

The sources of the strains studied and the fates of their last hosts are shown in table 7. All of the patients recovered. The patients were treated on different days of illness; they were of different ages, and their illnesses, as measured by degree of involvement and of invasion of the blood were of varying severity. Different specific therapies were employed. On this account, the comparative effectiveness of the drugs cannot be inferred from the data on these cases. Since these observations were made, we have observed cases in which the organisms were unaffected by one of the drugs in concentrations usually accepted as satisfactory but in which a different drug, shown to be more efficacious by in vitro tests, has been successfully employed.

Some of the factors making for recovery from pneumococcic infection after treatment with sulfonamide drugs are in the individual case, such as duration of illness, duration of administration, responsiveness of tissues both humoral and cellular, integrity of tissues, especially the kidneys and liver, and inhibitors in the blood or exudates, while other factors are more particularly related to the concentration of the sulfonamide compound maintained, its penetrability, toxicity and conversion and the damage done during excretion. In the clinical application of sulfonamide compounds it is necessary to consider the extent of the invasion, the previous experience of the invading strain and the immunity, active or passive, currently produced by the host. The concentration of organisms in the lungs as revealed by the examination of sputum may be as important as the degree of invasion of the blood. This is suggested by the observations on sputum of Frisch,[7] as well as by the inability to effect sterilization in heavily infected serous cavities or ulcerated areas, such as the cardiac valves.

CONCLUSIONS

The sulfonamide drugs differ in pneumococcidal and pneumococcostatic activity. Usually sulfathiazole and sulfapyridine in a concentration of 5 mg. per hundred cubic centimeters are equally active in destroying pneumococci. Sulfathiazole is more active against pneumococci than sulfadiazine in equal concentration, and than sulfathiazoline, sulfanilamide or sodium sulfanilyl sulfanilate. Neoarsphenamine is totally ineffective against pneumococci, while sulfadiazine, sulfathiazole and sulfapyridine are extremely effective. The concentration of organisms, as measured by the inoculum, and the concentration of the drug achieved and maintained are important factors influencing the therapeutic activity of the sulfonamide compounds. Very large inoculums were not sterilized by the concentrations usually employed clinically. Strains of pneumococci of the same type differed in their resistance to the same sulfonamide drugs in identical concentrations in vitro.

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CAPILLARY FRAGILITY IN RELATION TO DIABETES MELLITUS, HYPERTENSION AND AGE

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In the course of investigating diabetic retinitis, many instances of increased capillary fragility were noted in the absence of blood dyscrasia or obvious vitamin C deficiency. For this reason it was considered important to investigate capillary fragility in diabetes, since the literature contains no record of such a study. Reported methods of determining this vascular abnormality vary so widely in technic and in interpretation that it was deemed necessary to evaluate the known methods before undertaking this investigation.

Capillary fragility is usually determined by one of two methods, either negative or positive pressure being used. The first method, introduced by Hecht,[1] consists essentially in application of negative pressure over a standard area of skin for a given period of time. Most of the subsequent investigators [2] have used a procedure in which a glass cup, 10 to 28 mm. in diameter at the mouth, is pressed for one minute against the skin and the pressure within is reduced by a suction pump to a given degree of negative pressure, which is measured by an anaeroid or mercury manometer. The pressure at which petechiae appear is considered the level of fragility. It is found that the capillary fragility varies considerably with the site of the cutaneous area tested. Hecht states that the fragility is less over the back and on the extensor surfaces of the arms. The end points considered as positive are also variable. Dalldorf [3] originally advised the determination of the pressure "necessary to produce several macroscopic petechiae easily seen with the unaided eye." O'Hara and Hauch,[4] however, said: "Later it was decided [on the basis of a conference with Dalldorf] to adopt as the threshold reading the lowest negative pressure which, on casual inspection, gave an immediate impression that bleeding had occurred." Of their positive reactions about 80 per cent included 7 to 25 petechiae. As a rule, in readings which were considered negative there were from 0 to 10 petechiae.

Dalldorf,[3] in attempting to standardize the procedure, considered 30 mm. as the average pressure for the outer position of the arm, and Elliott [5] reported a negative pressure of 20 to 35 mm. of mercury as the normal range in the antecubital fossa. It has been stated that variations can occur before menses,[2c] with the climacterium,[2c] with psychic influences,[2a] with age,[2c] with the season [6] and with the hour of the day.[6] Moreover, even at a given time Roberts and her associates [6] have noted such variations in the two arms that they have averaged the readings of the two.

Most disturbing is the fact that O'Hara and Hauch [4] found that in the same subject the capillary resistance varies considerably at a given time in contiguous areas of skin and in the same area from day to day.

In view of these irregular findings, it was felt necessary to check this method. An apparatus was made consisting of a glass cup 1 cm. in diameter, a hand pump and a mercury manometer. In performing the test precaution was taken not to pull the cup away from the skin until atmospheric pressure was restored in the interior of the cup. Tests were performed on

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2. (*a*) Da Silva-Mello, A.: Die Wandresistenz der Blutkapillaren, München. med. Wchnschr. **76**:1717, 1929. (*b*) Brock, J., and Malcus, A.: Ueber die Capillarresistenz im Kindesalter, Ztschr. f. Kinderh. **56**:237, 1934. (*c*) Schrader, R.: Ueber Veränderungen im Vorhalten der Dichte der Kapillarwandung und deren Nachweis durch das Endothelsymptom, Mitt. a. d. Grenzgb. d. Med. u. Chir. **34**:260, 1921.

3. Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933.

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5. Elliott, R. H. E.: The Use of the Suction Test for Capillary Resistance in Thrombocytopenic Purpura, J. A. M. A. **110**:1177 (April 9) 1938.

6. Roberts, L. J.; Blair, R., and Bailey, M.: Seasonal Variations in Capillary Resistance of Institution Children, J. Pediat. **2**:626, 1937.

hospitalized patients selected at random. The test on a given patient was performed at one sitting unless otherwise noted, and the number of petechiae at one or more pressure levels was noted.

Table 1 illustrates some of the results obtained with this method. It is evident that the test is not consistent or reliable, since contiguous areas of one arm at the same time show marked variations. For example, patients S. C., B. K. and L. G. showed variations in the number of petechiae produced as a result of repeated tests at the same pressure. I. R., R. D. and F. G. had fewer petechiae at greater negative pressures than at smaller negative pressures.

TABLE 1.—*Capillary Fragility in Nondiabetic Nonhypertensive Patients Determined by Negative Pressure Method*

	Number of Petechiae at Negative Pressure of						
Name	10 Mm. Hg	15 Mm. Hg	20 Mm. Hg	25 Mm. Hg	30 Mm. Hg	35 Mm. Hg	40 Mm. Hg
R. P.	..	1	3	1	3	3	..
S. C.	1*	12	Innum-	..	..	..	..
	7	3	erable				
	9						
I. R.	1	10	13	4	11	3	14
		6					
R. D.	..	1	6	0	8	..	..
			7	1			
F. P.	..	..	5	0	0	0	2
			0	0	12	4	3
					3		
L. R.	..	3	0	10	3	0	1
				3			
F. G.	0	6	0	8	0	Innum-	..
		4				erable	
B. K.	8	3	0	2	20	..	..
	4						
	1						
L. G.	15	..	..	..	..	..	..
	4						

* Multiple readings indicate tests on contiguous areas.

The positive pressure technic of Rumpel [7] (1909) and Leede [8] (1911) was therefore investigated. This consists in raising the venous and capillary pressure of the arm by means of a tourniquet or a Riva-Rocci cuff. The appearance of macroscopic capillary ruptures (petechiae) is the end point. All subsequent investigators were careful to define the conditions under which their test was carried out. The time of compression is either five minutes (Brock,[2b] Schrader [2c]) or fifteen minutes (Gothlin,[9] Wright [10]). The pressure used varies considerably: 35 mm., 50 mm., to a point where "pulse is still palpable" [2b] or exactly between the systolic and the diastolic pressure.[10] The place of observation is the whole arm below the tourniquet or a circumscribed area, such as the antecubital fossa,[9] or a 2.5 cm. circle 4 cm. below the crease of the elbow on the flexor surface of the forearm.[10] The reading, usually done by good daylight or its equivalent, is either qualitative [2c] or quantitative.[11] It is of interest that none of the various authors stated whether single or repeated tests were used in drawing conclusions concerning the capillary fragility.

Bell and his co-workers [12] compared the results obtained on apparently healthy medical students with both positive (Gothlin) and negative (Dalldorf and Russell) pressure methods. They concluded that the results of each of the tests were consistent within themselves but that the results given by the two methods were not comparable. They suggested that possibly the two methods determine different functions of the capillaries. They were unable, however, to decide which of the two methods is to be preferred.

The method of Gothlin [9] was considered impractical by us, first, because the positive readings consist of small numbers of petechiae (2 to 6), which increases the chances of error through misinterpretation; second, because it requires using as many as three fifteen minute tests at three successively increased pressures for a given patient at one sitting. It is time consuming and may be frequently objected to by the patient.

Therefore, the following two methods were used in the present study:

(*a*) The qualitative-diastolic method. This consists of compressing the upper arm by a Riva-Rocci cuff for fifteen minutes at the patient's diastolic pressure. An estimate of the petechiae below the cuff was classified as "negative, slightly positive or definitely positive."

(*b*) The Wright modification of Gothlin's technic. This consists in application of a Riva-Rocci cuff to the upper arm for fifteen minutes (unless otherwise indicated) at a pressure half-

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11. Brock,[2b] Gothlin,[9] Wright and Lilienfeld.[10]

12. Bell, G. H.; Lazarus, S.; Munro, H. N., and Scarborough, H.: Capillary Fragility (Resistance): Negative and Positive Pressure Test Compared, Lancet **2**:536, 1942.

way between the patient's systolic and diastolic pressure. The petechiae were counted in a 2.5 cm. circle on the flexor surface of the arm 4 cm. below the crease of the elbow after waiting two to four minutes to allow the arm to regain its normal color. For a small number of patients fifteen minutes was intolerably long (especially at higher pressures) because of discomfort in the arm below the cuff. The readings were interpreted as follows: 0 to 20 petechiae as negative and over 20 as positive. In analyzing our results it was found useful to subdivide the positive readings into those with less and those with more than 50 petechiae. It may be of interest to mention that both the control and the diabetic patients usually showed small distinct petechiae, in contradistinction to the large confluent petechiae observed in persons with thrombopenic purpura and other blood dyscrasias.

Table 2 gives the results of positive pressure tests repeated over a period of one or more months on a group of diabetic patients. There was a variation in the results obtained in the same patient at different times, but this variation was greater in the case of the qualitative-diastolic method. The latter could be used, however, if sufficient numbers of tests were performed. Wright's method gave more uniform results. Accordingly, with this procedure a smaller number of tests are required.

In the study of the state of capillary fragility in diabetic patients it was deemed necessary to evaluate carefully the effect of age and of hypertension on the test. The presence of hypertension is especially important, since the height of the pressure at which the test is carried out varies with the blood pressure. Since neither Wright nor subsequent investigators have mentioned these factors, an independent control group was used.

RESULTS

In chart 1 are shown results based on a positive reaction with 20 petechiae or over and 1 with 50 petechiae or over. Capillary fragility was determined for 39 diabetic and 46 nondiabetic patients. All the patients were ambulatory, and none had hypertension or other complications. The diabetes was of long duration and varied both in severity and in state of control. The percentage of patients who showed increased capillary fragility reached a peak in the fifth and sixth decades in both groups. There was a greater incidence of increased capillary fragility in the diabetic as compared with the nondiabetic patients. It is interesting to note that similar

TABLE 2.—*Capillary Fragility in Diabetic Patients*

Name	Age	Systolic and Diastolic Blood Pressure, Mm. Hg	Qualitative Diastolic Method: Number of Observations: Negative	Slightly Positive	Positive	Period of Observation	Wright Method: Number of Observations: 0-10 Petechiae	20-50 Petechiae	50 Petechiae	Period of Observation
F. G.	55	190/ 70	0	2	1	5 months	0	0	4	2 months
E. G.	69	180/100	4	8	3	13 months	0	2	1	1 month
C. P.	67	150/ 80	3	4	3	10 months	0	1	4	2 months
A. K.	44	135/ 85	2	0	0	1½ years	0	2	1	1 month
R. P.	50	140/ 80	2	2	4	1 year	0	0	6	4 months
M. R.	54	135/ 75	8	5	4	15 months	1	0	4	4 months
A. S.	52	135/ 75	12	17	3	1 year	0	0	2	.....
R. B.	53	140/ 80	7	12	3	10 months	0	1	2	1 month
S. P.	61	185/ 90	..	..	..	.....	1	5	3	2 months
S. W.	61	125/ 70	..	..	..	.....	0	0	7	8 months
G. L.	63	150/ 70	..	..	..	.....	0	0	4	3 months
S. B.	57	125/ 65	..	..	..	.....	0	0	6	4 months
F. D.	55	145/ 80	..	..	..	.....	0	0	7	8 months
F. G.	50	120/ 70	2	5	7	14 months	..	..	..	.....
F. G.	59	150/ 80	1	0	2	3 months	..	..	..	.....
B. N.	50	135/ 90	9	3	0	1 month	..	..	..	.....
B. S.	67	145/ 80	12	1	..	14 months	..	..	..	.....
E. S.	70	180/ 90	1	0	2	6 weeks	..	..	..	.....

TABLE 3.—*Capillary Fragility in Diabetic Hypertensive Patients Determined Simultaneously at Test Pressure Levels of 100 Mm. of Mercury and Midway Between Systolic and Diastolic Pressure*

Name	Age	Systolic and Diastolic Blood Pressure, Mm. Hg	Number of Petechiae: At Pressure Halfway Between Systolic and Diastolic	At Pressure of 100 Mm. Hg
A. R.	60	160/ 90	135	46
H. S.	74	180/100	200	4
M. W.	58	160/ 95	63	120
L. S.	70	165/ 85	80	120
B. W.	71	165/ 85	140	0
A. O.	68	260/130	200	13
A. C.	58	180/100	200	100
N. T.	67	200/100	180	25
J. G.	70	210/ 90	56	45
S. F.	61	240/120	200	70
E. G.	69	180/105	400	170
I. C.	60	185/ 90	180	13
Percentage of patients with 50 petechiae or over			100	42

curves were obtained when 20 petechiae (Wright) and 50 petechiae were taken as the basis of a positive result.

Chart 2 shows the results obtained in a study of the capillary fragility in 54 diabetic patients

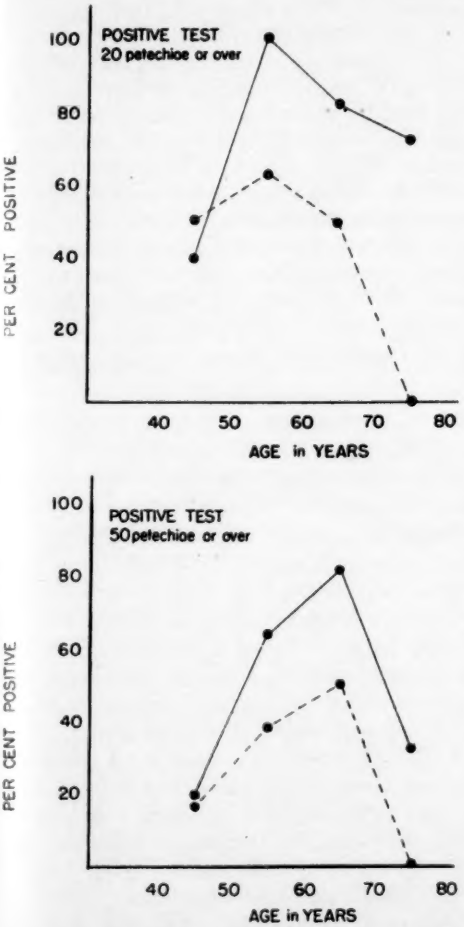

Chart 1.—Frequency of increased capillary fragility in 39 diabetic (solid line) and 46 nondiabetic (broken line) patients in relation to age.

(15 with hypertension) and 67 nondiabetic patients (21 with hypertension). Of the hypertensive patients with diabetes, 100 per cent showed increased capillary fragility, as compared with 53 per cent of the hypertensive patients without diabetes. Similarly the nonhypertensive patients with diabetes showed a higher incidence of increased capillary fragility (54 per cent) than those without diabetes (24 per cent). It is also evident that the subjects with hypertension showed a greater incidence of increased capillary fragility (53 per cent) than those without hypertension (24 per cent).

Since the pressure level at which the tourniquet test is carried out is higher in the case of hypertensive subjects (when the point midway between systolic and diastolic pressures is used), a comparison of the results at a lower pressure level (namely 100 mm., which is comparable to that used for nonhypertensive subjects) with those at higher levels was made. On 12 diabetic patients with hypertension such an experiment was performed as follows: On one arm the tourniquet test was performed at a pressure of 100 mm. and on the other at the usual higher level.

As shown in table 3, all patients exhibited increased capillary fragility at the higher pressure and only 42 per cent at the lower pressure (50 petechiae being used as the end point). Referring to chart 2, it is noted that of the diabetic patients without hypertension, whose test pressure was about 100 mm. of mercury, 54 per cent had a positive reaction to the tourniquet test, while of the diabetic patients with hypertension only 42 per cent had a positive reaction to that test (table 3) at the same pressure level of 100. This suggests that in the case of hypertensive patients the level of pressure at which the test is performed rather than the tension per se is respon-

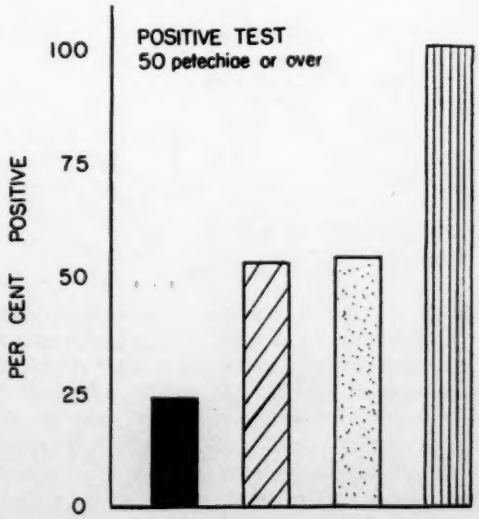

Chart 2.—Frequency of increased capillary fragility in 39 nondiabetic nonhypertensive patients (solid bar), 45 nondiabetic hypertensive patients (diagonal lines), 21 diabetic nonhypertensive patients (dots) and 15 diabetic hypertensive patients (vertical lines).

sible for the high percentage of positive reactions to capillary fragility tests. Further study is necessary to determine the proper pressure at

which the tourniquet test should be performed on hypertensive persons for the determination of capillary fragility.

The results shown in chart 2 indicate that, irrespective of the validity of the fragility test in the presence of hypertension, there is a definitely increased capillary fragility in diabetic patients as compared with nondiabetic persons of the same age. Further, from chart 1 it is evident that the incidence of increased capillary fragility in persons with diabetes parallels that of nondiabetic subjects with increasing age.

CONCLUSIONS

Various methods for measuring capillary fragility have been investigated. Negative pressure methods were found to be unreliable. Of the positive pressure methods tried on a group of diabetic patients, Wright's method gave the most reliable results.

A group of 54 adult patients (15 with hypertension) and 67 nondiabetic patients (21 with hypertension) were tested by Wright's method. The incidence of increased capillary fragility was greatest in the fifth and sixth decades. The diabetic patients showed a greater incidence of increased capillary fragility at each age decade than the nondiabetic subjects.

In diabetic hypertensive patients the test showed a greater incidence of increased capillary fragility at the higher pressure levels (midway between systolic and diastolic pressure), as used by Wright, than at a lower arbitrary level (100 mm. of mercury) when performed simultaneously on the two arms.

Without further study no conclusions can be drawn concerning the proper pressure at which the positive pressure test should be performed on hypertensive patients.

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VITAMIN THERAPY IN INCREASED CAPILLARY FRAGILITY OF DIABETES MELLITUS

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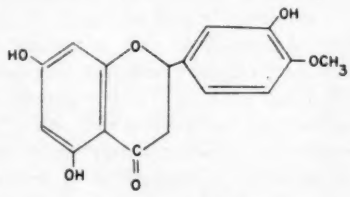
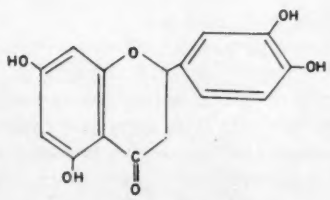
In 1936 Szent-Györgyi and his associates [1] isolated a crystalline substance from lemons which they called citrin. They [1a] found that this substance corrected the increased capillary fragility in guinea pigs on a scorbutogenic diet and in human beings with certain pathologic conditions. They called it vitamin P. Subsequently, studies both on animals and on human beings were carried out by numerous investigators. It was shown that citrin, a flavanone glucoside, is composed of two fractions, hesperidin glucoside [2] (formula I shows the aglycone), which is insoluble in water and is stable, and eriodictyol glucoside (formula II shows the aglycone), which is water soluble and sensitive to oxidation. Eriodictyol is demethylated hesperidin and contains the unstable orthohydroquinone group. It has been reported [1b] that the relative amounts of these substances in citrin vary with the ripening of the fruit used in its preparation and with the method of isolation. However, in most of the publications concerning therapy no indication of the relative amounts of the two fractions in citrin prepared according to Szent-Györgyi's method is given. It has also been shown that hesperidin is readily converted by alkali to the open ring chalcone (3,2′,4′,6′-tetrahydroxy-4-methoxychalcone glucoside).[3] Wawra and Webb [3a] postulated that hesperidin in this form is attached to protein through the α, β unsaturated ketonic group. They suggested that the chalcone is the biologically active component of citrin. They have further shown that after conversion of hesperidin to the chalcone by treatment with



HESPERIDIN AGLYCONE I



ERIODICTYOL AGLYCONE II

alkali in the cold the chalcone may be precipitated by acidification and that in crystalline form it slowly reverts to hesperidin. If the chalcone is indeed the biologically active constituent of citrin, the results of therapeutic tests with hesperidin depend to a large extent on the manner in which it is handled, such as treatment with alkali at some stage in its isolation, the length of time it stands in crystalline form or in solution before use, and whether the oral or the intravenous route of administration is employed. These factors may be considered, in part, as a

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1. (*a*) Rusznyak, S., and Szent-Györgyi, A.: Vitamin P: Flavonols as Vitamins, Nature, London **138**:27, 1936. (*b*) Armentano, L.; Bentsath, A.; Beres, T.; Rusznyak, S., and Szent-Györgyi, A.: Ueber der Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren. Vitamin P, Deutsche med. Wchnschr. **62**:1325, 1936. (*c*) Szent-Györgyi, A.: Methoden zur Herstellung von Citrin, Ztschr. f. physiol. Chem. **255**:126, 1938.

2. (*a*) Bruckner, V., and Szent-Györgyi, A.: Chemical Nature of Citrin, Nature, London **138**:1057, 1936. (*b*) Wilson, C. W.: A Study of the Boric Acid Color Reaction of Flavone Derivatives, J. Am. Chem. Soc. **61**:2303, 1939.

3. (*a*) Wawra, C. Z., and Webb, J. L.: The Isolation of a New Oxidation—Reduction Enzyme from Lemon Peel (Vitamin P), Science **96**:302, 1942. (*b*) Wilson.[2b]

reason for the conflicting reports on the efficacy of vitamin P therapy.

In addition, in observations on man, the effectiveness of the therapy has been judged to a large extent by the result of some type of capillary fragility test. In the reports in which the method of measurement is given, the negative pressure method, which we consider unreliable, was commonly used (table 1).

In a previous communication [4] we have discussed the pitfalls of interpretation of data obtained by the various methods for determining capillary fragility, which explain in part the discrepancies in the literature as to the therapeutic results. The negative pressure method was found to be unreliable because of the variability of the findings in the same patient at a given time. The Wright positive pressure method can be utilized only if age and blood pressure are taken [4] into consideration in accordance with findings previously pointed out.

A review of the literature (table 1) indicates that citrin was tried in a wide variety of cases with increased capillary fragility irrespective of the underlying disease. For example, it was used in treatment of such widely differing syndromes as tuberculosis, pleurisy, myxedema and multiple myeloma. Conclusions of doubtful validity were drawn from some cases in which clinical bleeding alone was used as a criterion of therapeutic effectiveness, many of them cases of self-limited diseases, such as measles, arsenic intoxication and nephritis.

This is a report of the effects of various substances containing vitamin P and of purified components of citrin, hesperidin and eriodictyol in diabetic patients with increased capillary fragility as measured by positive pressure methods. Most of the preparations were given orally, but to a few long and well studied diabetic patients the purified hesperidin and eriodictyol were administered intravenously. In addition, the increased capillary fragility in 2 cases of thrombopenic purpura and in 1 case of rheumatoid arthritis was treated by intravenous injection of hesperidin and eriodictyol.

METHODS

To determine capillary fragility the Wright [5] quantitative positive pressure method was used. These observations were subject to the reservations for patients' age and blood pressure which were pointed out in a previous communication.[4] For a preliminary series of patients the qualitative positive pressure test, in which the diastolic pressure was maintained for fifteen minutes and an estimate made of the number of petechiae on the forearm and dorsum of the hand, was used in determining a negative, slightly positive or markedly positive result.

Patients exhibiting an increased capillary fragility were used as test subjects. Before therapeutic tests were undertaken, the presence of increased capillary fragility was confirmed by repeated tests performed over a period of at least several weeks and in some cases many months. All of the patients had diabetes, except for 2 with thrombopenic purpura and 1 with rheumatoid arthritis.

A course of vitamin C therapy was instituted before vitamin P therapy was undertaken except for 2 patients, both of whom had a normal level of vitamin C in the plasma.[6] The dissociation between the therapeutic effects of vitamins C and P has been emphasized by Scarborough and his associates [7] and also observed by Shwachman and Gould.[8] The latter found that vitamin C administered to scorbutic guinea pigs stimulated the phosphatase-producing centers, but they failed to obtain this with our preparations of eriodictyol and hesperidin,[9] which they gave intraperitoneally, singly and in combination.

In one series an exhaustive course of oral administration of vitamins C and B complex [10] was given before treatment with vitamin P was started. Vitamin P was administered in several forms,[10] as follows:

1. Fresh lemon juice.

2. Fresh crude lemon–hot water extract, given orally according to the method recommended by the research laboratory of the California Fruit Growers' Exchange.[11]

3. Tablets containing 0.25 Gm. of hesperidin, given orally (found by the hot alkali test [12] to contain only traces of eriodictyol).

4. Hesperidin which was prepared in crystalline form from the finely powdered tablets by a continuous extraction with hot diethylene dioxide (dioxane) and crystallization from diethylene dioxide and acetone as fine pale yellow crystals. These gave a negative reaction for eriodictyol with hot potassium hydroxide solution. This

4. Beaser, S. B.; Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes Mellitus, Hypertension and Age, Arch. Int. Med., this issue, p. 18.

5. Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Vitamin C, Arch. Int. Med. **57**:241 (Feb.) 1936.

6. Blood vitamin C was determined as plasma ascorbic acid by the method of R. L. Mindlin and A. M. Butler (The Determination of Ascorbic Acid in Plasma: A Macromethod and Micromethod, J. Biol. Chem. **122**: 673, 1938). The normal range of plasma ascorbic acid during fasting was considered 0.8 to 1.4 mg. per hundred cubic centimeters of blood.

7. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610, 1938.

8. Shwachman, H., and Gould, B. S.: Serum Phosphatase in Experimental Scurvy, J. Nutrition **23**:271, 1942.

9. Shwachman, H., and Gould, B. S.: Personal communication to the authors.

10. Vitamin C tablets and vitamin B complex capsules were supplied by the Hoffmann-LaRoche, Inc., of Nutley, N. J.; hesperidin tablets, by Glaxo Laboratories Ltd., of Greenford, England, through Ayerst, McKenna and Harrison Ltd., of Montreal, Canada, and calcium eriodictate, by Abbott Laboratories, North Chicago, Ill.

11. Lorenz, A. J., and Arnold, L. J.: Personal communication to the authors.

12. Huszák, S.: Ueber das Schicksal parenteral einverleibter Citrinlösung in Tierkörper, Ztschr. f. physiol. Chem. **249**:214, 1937.

TABLE 1.—*Summary of Reports on the Use of Vitamin P Clinically*

Disease	Preparation, Method of Administration and Dosage	Test Method	Therapeutic Effectiveness	Number of Cases	Author	Comments Concerning Capillary Fragility
1. Vascular purpura	Citrin solution intravenously, 20-40 mg. per day for 8-12 days	Negative pressure	Good	3	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Negative pressure method unreliable
2. Vascular purpura	Citrin solution intravenously	Clinical bleeding	Good	2	Lajos, S.: Klin. Wchnschr. **16**: 1615, 1937	Unreliable test method
3. Vascular purpura	Citrin solution intravenously, 50 mg. per day for 6 weeks	Negative pressure	Good after 6-10 weeks	..	Jersild, T.: Lancet **1**: 1445, 1938	Negative pressure method unreliable and question of spontaneous remission
4. Thrombopenic purpura	Citrin solution intravenously, 20-40 mg. per day for 8-12 days	Negative pressure	Equivocal	4	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Negative pressure method unreliable
5. Thrombopenic purpura	.....	Clinical course	None	..	Rosenthal, N.: J. A. M. A. **112**: 101, 1939	
6. Thrombopenic purpura	Citrin solution intravenously, 50 mg. twice in 4 weeks	"Tourniquet test" of capillary fragility and platelets	None	..	Vaughan, M.: Brit. M. J. **2**: 842, 1937	
7. Thrombopenic purpura	Citrin solution and vitamin C, intravenously	Bleeding time and platelet counts	Good	3	Decker, C. T.: München. med. Wchnschr. **86**: 292, 1939	Unreliable method
8. Thrombopenic purpura	Citrin solution intravenously, 25-60 mg. per day and orally 25 mg. per day	Negative pressure	Good	2	Vacek, V.: Schweiz. med. Wchnschr. **71**: 155, 1941	Negative pressure method unreliable
9. Leukemia	Citrin orally, 50 mg. per day	Development of petechiae	Good	2	Vacek: Ibid.	Unreliable test method, no follow-up
10. Multiple myeloma	Citrin solution intravenously, 40 mg.	Clinical bleeding	Stopped for 2 days	..	Vacek: Ibid.	Unreliable test method
11. Vitamin deficiency purpura	Hesperidin tablets orally, 1 Gm.	Negative pressure	Good	6	Scarborough [7]	Negative pressure method unreliable
12. Vitamin deficiency purpura	Citrin solution intravenously, 50 mg. per day	Clinical bleeding	Good	..	Jersild, T.: Lancet **1**: 632, 1939	Unreliable test method
13. Infectious diseases; measles	Hesperidin tablets orally, 0.25 Gm. every 2 hours	Clinical bleeding	Good in 24 hours	..	Miller, A. A.: Brit. J. Child. Dis. **38**: 1, 1941	
14. Endocarditis	Citrin solution intravenously, 20-40 mg. for 8-12 days	Negative pressure	Equivocal	..	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method
15. Staphylococcic sepsis; peritonitis; tuberculosis; pleurisy	Citrin solution intravenously, 20-40 mg. for 8-12 days	Negative pressure	Equivocal	3	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method
16. Arthritis	Citrin solution intravenously, 20-40 mg. for 8-12 days	Negative pressure	Equivocal	..	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method
17. Nephritis	Citrin solution intravenously, 20-40 mg. for 8-12 days	Negative pressure	Equivocal	..	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method
18. Hemorrhagic nephritis	Citrin solution intravenously, 25-50 mg.	Urinary bleeding	Shortened course	..	Lajos, S.: Klin. Wchnschr. **16**: 1615, 1937	Unreliable test method
19. Hemorrhagic nephritis	Citrin solution intravenously, 30 mg. for 2-4 days	Count of urine red blood cells	None	7	Gimsing, T.: Ugesk. f. læger **101**: 117, 1939	Unreliable test method
20. Ulcerative colitis	Citrin solution intravenously and citrin orally, 20-150 mg.	Rectal bleeding	Good	..	Vacek, V.: Schweiz. med. Wchnschr. **71**: 155, 1941	Unreliable test method
21. Arsenic poisoning	Hesperidin tablets orally, 0.25-1.0 Gm. for 4-8 days	Negative pressure	Good	2	Horne, G., and Scarborough, H.: Lancet **2**: 66, 1940	Unreliable test method
22. Arsenic poisoning	Hesperidin tablets orally, 0.25-1.0 Gm. every 2 hours	Urinary bleeding	Good	..	Gorrie, D. R.: Lancet **1**: 1005, 1940	Unreliable test method
23. Myxedema	Citrin solution intravenously, 20-40 mg. per day for 8-12 days	Negative pressure	Equivocal	..	Armentano, Bentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method
24. Increased capillary fragility in children	Calcium eriodyctate orally, 25 mg. per day for 1 week or more	Positive pressure (Wright), 40-75 petechiae	Equivocal	6	Rapaport, H. G., and Klein, S.: J. Pediat. **18**: 321, 1941	Variations during control periods were considerable and not very positive at onset
25. Diabetes	Citrin solution intravenously, 20-40 mg. per day for 8-12 days	Negative pressure	None	2	Armentano, Gentsath, Beres, Rusznyak and Szent-Györgyi [1b]	Unreliable test method

material was given intravenously as a freshly prepared solution of 300 mg. in 0.2 normal sodium hydroxide solution (2 cc.) sterilized by heating at the boiling point for one minute just before administration.

5. Eriodictyol as the calcium salt, which was dissolved in water just before intravenous administration. This orange-brown powder gave a strongly positive red color with hot potassium hydroxide solution, confirmatory of the presence of eriodictyol.

RESULTS

The first group studied consisted of 4 diabetic patients who had in common a definitely increased capillary fragility and no other discernible disease, even hypertension. After a control period of determinations of capillary fragility they were treated successively with vitamin C given orally (see table 2), vitamin P given orally (hesperidin tablets) and a combination of the two. No significant change in the capillary fragility was noted on repeated tests as a result of this oral therapy. It is noteworthy that in 2 patients who had a low level of vitamin C in the blood a rise of this level to normal was not accompanied by improved capillary fragility.

The second group consisted of 6 diabetic patients with retinitis and increased capillary fragility treated for many months with large oral doses of vitamin C and vitamin B complex and lemon juice as a source of vitamin P. The capillary fragility, followed by the qualitative method, showed no improvement as a result of this therapy (table 3). In the 4 cases in which determinations of blood vitamin C were made prior to the institution of the therapy, the values were normal. Saturation of the patients with vitamin C was confirmed by repeated determinations of urinary vitamin C during the course of treatment. In spite of high levels of excretion, which indicated saturation, capillary fragility remained uninfluenced. No demonstrable effect on the retinitis was noted.[13]

The third group consisted of 6 patients: 3 with diabetes, 1 with rheumatoid arthritis, 1 with primary thrombopenic purpura and 1 with thrombopenic purpura secondary to aplastic

TABLE 2.—*Effect of Vitamin C and P Therapy* on Increased*

	Age	Blood Pressure, Mm. Hg	Pressure at Which Test Was Performed, Mm. Hg	Capillary Fragility Test (Wright), No. of Petechiae: Before Treatment	Capillary Fragility Test (Wright), No. of Petechiae: One Month Later	Vitamin C Therapy for 2 Weeks, Mg. Ascorbic Acid per Day	Blood Vitamin C Levels: Before Therapy	Blood Vitamin C Levels: After Therapy
1	55	140/80	95	100	200	200	0.36	1.5
2	57	125/65	95	105	150	200	0.42	1.4
3	61	125/70	100	150	125	0	1.2	...
4	63	150/70	115	200	200	0	1.1	...

* From left to right, this table is a chronologic record of successive therapeutic trials.

TABLE 3.—*Effect of Vitamin Therapy (C, B, P) on Increased Capillary Fragility in Diabetic Patients*

	Name	Age	Blood Pressure, Mm. Hg	Fasting Initial Blood Vitamin C, Mg. per 100 Cc.*	Capillary Fragility Test (Qualitative Method) Before Treatment	Oral Treatment †: Vitamin C: Mg. Daily	Vitamin C: Duration of Therapy, Weeks	B Complex ‡: Capsules Daily	B Complex ‡: Duration of Therapy, Weeks	Lemon Juice: Lemons Daily	Lemon Juice: Duration of Therapy, Weeks	Capillary Fragility Test (Qualitative Method) After Vitamin Treatment
5	B. L.	44	120/ 80	...	Positive	300	6	3	24	1	8	Positive
						150	15					
6	F. G.	50	130/ 80	0.9	Positive	150	4	3	3	2	6	Positive
						200	2	6	29			
						400	6					
7	C. P.	67	160/ 80	0.9	Positive	300	5	3	6	1	5	Positive
8	E. G.	69	180/100	1.0	Positive	100	1	6	7	12	6	Positive
						150	2	3	2			
9	R. P.	50	140/ 80	0.9	Positive	300	6					
						300	1	6	12	2	3	Positive
						500	5			4	3	
										1	11	
10	M. R.	54	130/ 80	...	Positive	200	1	3	14	2-3	9	Positive
						400	2			2	10	
						100	1					
						300	6					

* Blood vitamin C was determined by the method of Mindlin and Butler.[6]
† Vitamin C excretion in the urine on repeated examination was high in all cases.
‡ Beroeca B complex perles, containing the total components of natural vitamin B complex (including nicotinic acid and vitamin B_6 [pyridoxine] in potencies as found in dried brewers' yeast, 200 mg. per perle) and fortified with thiamine hydrochloride to total 300 U. S. P. units of vitamin B_1 and with riboflavin to total 100 micrograms per perle.

13. All these patients have been repeatedly examined ophthalmologically by Dr. E. E. Covitz, of the ophthalmologic clinic.

anemia (following use of anacin, a proprietary preparation containing acetophenetidin and acetylsalicylic acid with quinine sulfate and caffeine). Two of the diabetic patients (patients 9 and 10, tables 3 and 4) had previously received extensive oral therapy without benefit.

These patients all had abnormal capillary fragility. They were all given hesperidin intravenously, 3 received a course of intravenous injections of calcium eriodictate following the treatment with hesperidin, and 1 patient subsequently received, in addition, a combination of

Capillary Fragility in Nonhypertensive Diabetic† Patients

Capillary Fragility Test After Vitamin C Therapy, No. of Petechiae	No. of Weeks of Oral Vitamin P Therapy (Hesperidin 1 Gm. Daily)	Capillary Fragility Test After Vitamin P Therapy, No. of Petechiae	Combined Vitamin C and Vitamin P (Hesperidin) Therapy for 2 Weeks		Capillary Fragility Test After Cessation of Therapy, Number of Petechiae		
			Vitamin C Daily	Hesperidin Daily, Gm.	Immediately	Three Weeks	Four Months
150	3	72	200 mg. ascorbic acid	1	150	150	170
150	3	100	200 mg. ascorbic acid	1	85	70	...
...	3	120	6 oranges, 1 lemon	1	100	100	150
...	3	200	9 oranges	1	200	...	...

† Diabetes was moderately well regulated, and no patient had retinitis.

TABLE 4.—*Therapeutic Administration* of Vitamin P Intravenously*

	Name	Age	Diagnosis	Capillary Fragility† Before Therapy, Number of Petechiae	Hesperidin Therapy Intravenously, Mg. per Day	Capillary Fragility† After Hesperidin Therapy, Number of Petechiae	Calcium Eriodictate Therapy Intravenously, Mg. per Day	Capillary Fragility† After Calcium Eriodictate Therapy, Number of Petechiae	Calcium Eriodictate and Hesperidin Intravenously, Mg. per Day	Capillary Fragility† After Calcium Eriodictate and Hesperidin Therapy, Number of Petechiae
9	M. R.	56	Diabetic retinitis	100	200 for 10 days	120	100 for 10 days	120	.....	...
10	R. P.	51	Diabetic retinitis	200	200 for 9 days	200	100 for 10 days	200	100 of each for 10 days	160
11	M. R.	61	Diabetes; peripheral vascular disease	100	200 for 7 days	115	.....	...	.....	...
12	A. H.	52	Rheumatoid arthritis	150	200 for 10 days	80	.....	...	.....	...
13	J. F.	56	Primary thrombopenic purpura	200	200 for 9 days	200	100 for 12 days	200	.....	...
14	M. P.	32	Thrombopenic purpura; aplastic anemia	90	200 for 7 days	110	.....	...	.....	...

* From left to right, this table is a chronologic record of successive therapeutic trials.
† Capillary fragility was determined by the Wright positive pressure method.

the two intravenously. No beneficial effect was noted.

COMMENT

Our previous study[4] showed that capillary fragility varied with both age and the patient's blood pressure (which determines the pressure level at which the test is performed) but that the diabetic patients had a higher incidence of increased capillary fragility in each age group. We also noted that both the control and the diabetic patients usually showed small, distinct petechiae, in distinction to the large, confluent petechiae observed in persons with thrombopenic purpura and other blood dyscrasias.

So far no explanation has been found for the increased capillary fragility in diabetes. It may be an exaggeration of a normal tendency in relation to age, and thus it may be another indication that diabetic patients are aging earlier. This does not reveal its pathogenesis. Since a deficiency in vitamins C and P was considered a possible cause of the increased capillary fragility in diabetic patients, it was necessary to check the diets of our patients for their content in vitamins C and P. No deficiency in the intake of these vitamins was found. The therapeutic results with vitamin C indicate that the increased capillary fragility in our patients could not be attributed to latent scurvy. This has been further proved by the normal level of vitamin C in the blood as well as the vitamin C saturation of the tissues as reflected in high urinary excretion of ascorbic acid. Impairment in the absorption of vitamin P was ruled out by the use of intravenous administration. Our negative results with vitamin P given orally confirmed the observations of previous investigators on its lack of effectiveness (table 1). It was therefore necessary to try in addition the administration of the two principal constituents of citrin, hesperidin and eriodictyol, intravenously, separately and combined. The negative results obtained in this experiment on a group of our patients add further proof of the ineffectiveness of vitamin P

on increased capillary fragility in the diseases mentioned. Hesperidin was given intravenously as a freshly prepared alkaline solution. It is probable that the greater part of the hesperidin existed under these conditions as the open ring chalcone, thought by Wawra and Webb [3a] to be the biologically active component of citrin.

SUMMARY

A review of the literature on the clinical use of vitamin P reveals that various forms of vitamin P have been used, but with no clear notion as to what component of citrin was being tested. Such therapy was studied in a wide variety of cases with increased capillary fragility irrespective of the underlying disease, which was frequently a self-limited disease. Conclusions of doubtful validity were drawn in some cases when the criterion of therapeutic effectiveness was clinical bleeding or the result of a negative pressure test for determining capillary fragility.

The effectiveness of oral administration of vitamin C and the B complex on the increased capillary fragility in diabetic patients with and without retinitis has been tested, with negative results.

The effectiveness of both orally and parenterally administered vitamin P in some patients of this group was studied. Both the hesperidin and the eriodictyol fraction of vitamin P were tested intravenously, separately and combined, with negative results.

A similar study of the effect of vitamin P therapy on the increased capillary fragility of thrombopenic purpura and rheumatoid arthritis was made, with negative results.

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INFLUENCE OF RESPIRATION ON BLOOD PRESSURE IN MAN

WITH A NOTE ON VASOMOTOR WAVES

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The study of the influence of respiration on the blood pressure has been based mainly on experiments with animals. Lewis [1] studied in cats the effect on the blood pressure of variations in the pericardial pressure, section of the vagi and differences in the type of respiration and concluded that the main factor was the decrease of the pericardial pressure during inspiration, which caused an increase of the blood pressure in this phase. His experiments on man [2] permitted him to observe the influence of the type and rate of respiration and of the pulse rate. He concluded that the blood pressure has no uniform behavior during the respiratory movement, because it can rise or fall according to the type, frequency and depth of respiration. During quiet breathing no respiratory modifications in arterial pressure were noted.

Visscher, Rupp and Scott [3] made experiments on dogs and came to the conclusion that there is an inspiratory increase of the blood pressure.

Katz and Gauchat [4] studied in animals the factors which contribute to the variations of pulse and blood pressure during deep breathing and ascribed primary importance to changes in pleural pressure.

Mouktar [5] observed an inspiratory fall in the blood pressure of rabbits and an expiratory rise. He obtained the same results with human subjects, by the use of the oscillometer of Pachon.

Hasegawa [6] in 1927 reported the influence of the type of respiration on the blood pressure. He noted an increase during inspiration with thoracic breathing and a decrease during the same phase with abdominal breathing.

From the Academia Nacional de Medicina, Instituto de Investigaciones Físicas aplicadas a la Patología Humana, Sección Cardiología. This study was aided by a grant from Próspero Baurin.

1. Lewis, T.: Studies of the Relationship Between Respiration and Blood Pressure, J. Physiol. **37**:213, 1908.

2. Lewis, T.: Studies of the Relationship Between Respiration and Blood Pressure, J. Physiol. **37**:233, 1908.

3. Visscher, M. B.; Rupp, A., and Scott, F. H.: The Respiratory Wave in Arterial Blood Pressure, Am. J. Physiol. **70**:586, 1924.

4. Katz, L. N., and Gauchet, H. W.: Observations on Pulses Paradoxus (with Special Reference to Pericardial Effusions): Experimental, Arch. Int. Med. **33**:371 (March) 1924.

5. Mouktar, A.: Les modifications de la pression artérielle sous l'influence de la respiration chez l'homme, Bull. Acad. de méd., Paris **92**:864, 1924.

6. Hasegawa, U.: Influences on Blood Pressure Curves by Volume of Air, Japan M. World **5**:99, 1925; abstracted, Arch. d. mal. du cœur **20**:182, 1927.

On the other hand, the vasomotor waves have been studied also almost exclusively in poisoned or semiasphyxiated animals.

Traube [7] experimented on curarized dogs with both vagi cut. Suspension of artificial respiration caused large waves in the arterial pressure which he attributed to rhythmic discharges from the respiratory center toward the vasomotor center.

Hering [8] noticed the same phenomena in dogs under similar conditions. His theory of the mechanism of the changes was identical with Traube's.

Later, Mayer [9] observed vasomotor waves in anesthetized but not curarized rabbits when respiration was interrupted or retarded. He discovered in his records another type of waves which he called "interference waves." These would be the result of interference of cardiac and respiratory waves.

Starling [10] observed the Traube-Hering waves when he stopped administering artificial respiration to dogs poisoned with morphine or curare. He attributed his results to the increased venosity of the blood of the vasomotor center. He stated that these waves had also been observed in cases of hemorrhage.

The results of the experiments on animals could not be entirely applied to human beings. On the other hand, the investigations on human subjects were made with unreliable methods, and very contradictory results were obtained by the different authors with regard to the influence of the respiration on the blood pressure.

These reasons have induced us to study this problem by means of registration of the intra-arterial pressure of human subjects. Registration of intra-arterial pressure has been used with human subjects by many workers (von Bonsdorff,[11] Hamilton, Brewer and Brotman,[12] Hamilton, Woodbury and Harper,[13] and others) in order to study other circulatory phenomena not related to respiration.

METHOD AND MATERIAL

For the determination of intra-arterial pressure, the Hamilton manometer [12] with a rubber membrane as required for an optical registration was used. The natural frequency of the system was between 60 and 80 oscillations per second. The calibration was made before and after each reading of blood pressure, and the pressure in the system was measured four or five times with a mercury manometer according to the blood pressure of the subject. The respiratory movements were registered simultaneously by means of a pneumograph connected to a Frank segmentary capsule.

These experiments were made on subjects whose cardiorespiratory system was normal and who were in recumbent position. The puncture was made in the humeral, axillary or femoral artery, a needle of 0.7 by 25 gage being used. The time was registered in fifths of a second, with a Jacquet chronometer.

7. Traube, L.: Centralbl. f. d. med. Wissensch. **3**:880, 1865; cited by Halliburton.[14]

8. Hering, E: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **60**:829, 1869; cited by Halliburton.[14]

9. Mayer, S.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **74**:281, 1876; cited by Halliburton.[14]

10. Starling, E. H.: Principles of Human Physiology, Philadelphia, Lea & Febiger, 1933.

11. von Bonsdorff, B.: Zur Methodik der Blutdruckmessung, mit besonderer Berücksichtigung der Registrierung absoluter Sphygmogramme beim Menschen, Acta med. Scandinav., 1932, supp. 51, p. 1.

12. Hamilton, W. F.; Brewer, G., and Brotman, I.: I. Analytical Description of a New High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intra-Cardiac Pressure; II. Pressure Pulse Contours in the Intact Animal, Am. J. Physiol. **107**:427, 1934.

13. Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Physiologic Relationships Between Intra-Thoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853 (Sept. 12) 1936.

We studied the relations between the blood pressure and the different respiratory types and obtained readings during apnea following deep breathing and apnea following normal expiration. We also studied the effect of the Valsalva test and the influence of coughing.

A total of 15 subjects were studied, and 40 records of intra-arterial pressure were obtained simultaneously with pneumographic records in order to study the respiratory waves. In 27 cases the pressure was taken in the humeral artery, and in 13, in the femporal artery.

Nineteen records were taken during normal breathing, 10 during deep breathing, 7 during deep thoracic breathing and 4 during both slow and fast abdominal breathing. In 4 cases records of intra-arterial pressure were made during the apnea following a deep breath. Six records were made after normal breathing, 2 with the Valsalva test and 5 when the subjects were coughing.

RESULTS AND COMMENT

Our investigations in man have permitted us to ascertain that under normal conditions two principal types of waves exist: (1) vasomotor waves that are independent of the respiratory movements and (2) waves coinciding with and depending on respiratory movements.

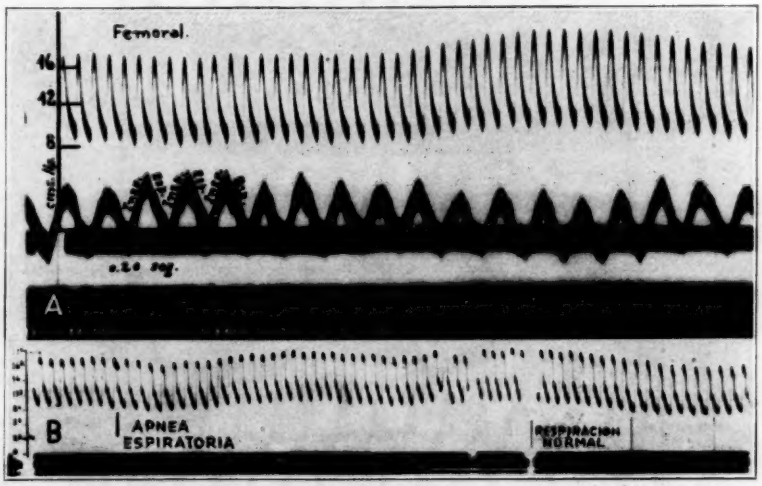


Fig. 1.—*A*, Traube-Hering vasomotor waves in a normal human subject. The tracing shows spontaneous vasomotor waves independent of respiratory phases. The rate of the waves is about 6 to 7 per minute. *B*, vasomotor waves which are more definite during and after the respiratory pause.

1. The vasomotor waves (Traube-Hering waves) are characterized by their low frequency (6 to 7 per minute) and their independence of respiration. They appear either during normal breathing (fig. 1 *A*) or during brief periods of apnea (fig. 1 *B*). Under the latter circumstances, the vasomotor waves become clearer and more frequent. They are also more evident when no respiratory variations of the blood pressure are noted. When the curve ascends, the maximal, medial and minimal pressures increase, and when the curve descends, the opposite occurs. The physiologic explanation of these curves is not as yet entirely clear. Possible causes could be:

(*a*) Rhythmic discharges from the vasomotor centers caused by accumulation of carbon dioxide in the blood. In this connection, Halliburton[14] admitted the

14. Halliburton, W. D.: Traube Waves and Mayer Waves, Quart. J. Exper. Physiol. **12**:227, 1920.

subjection of the vasomotor centers to the same chemical influences as the respiratory centers.

(*b*) Periodic discharges from the respiratory centers on the vasomotor centers (Traube,[7] Aalkjær,[15] Hering [8]). According to this theory, vasomotor waves might be of respiratory origin.

(*c*) Periodic contractions of the arteries caused by reflex action (variation in the sympathetic tone) or chemical stimulation (for instance, by tissular metabolites

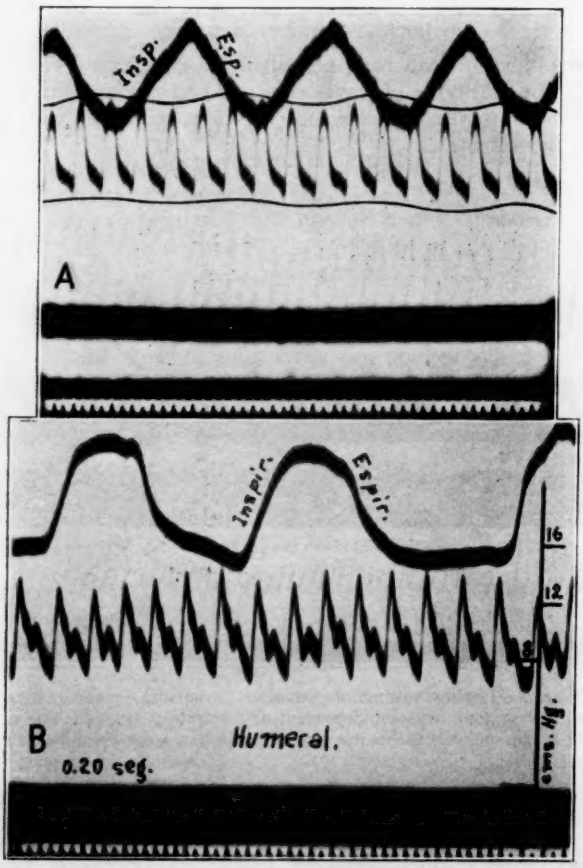


Fig. 2.—*A*, variations in blood pressure during ordinary breathing (respiratory waves). There are a fall during inspiration and a rise during expiration without changes in the cardiac rate. *B*, variations of blood pressure during deep, slow thoracic breathing. In this case an increase in the blood and the pulse pressure during expiration and the respiratory pauses may be noted.

and cholinergic or adrenergic substances). The respiratory and vasomotor centers are not involved.

15. Aalkjær, V.: Ueber Aussehen, Bildungsstelle und Ursache der Traube-Hering-Mayerschen-Blutdruckschwankungen, Skandinav. Arch. f. Physiol. **71**:301, 1935.

On suspension of respiration, Traube-Hering waves become clearer. Therefore, it is probable that they have a central origin and that the vasomotor centers are excited from the respiratory centers or by the tensional variation of the oxygen and carbon dioxide in the blood (hypoxemia and hypercapnemia). According to Halliburton [14] these would be the true vasomotor waves to which the name of Traube, their discoverer, should be given.

2. Respiratory waves are characterized by a rhythm synchronous with that of respiration.

The influence of the respiratory type, thoracic or abdominal, and the depth and velocity of the respiratory movements on the blood pressure were studied.

In 7 subjects no respiratory modifications were observed during ordinary breathing. An increase in the systolic and diastolic pressure during expiration

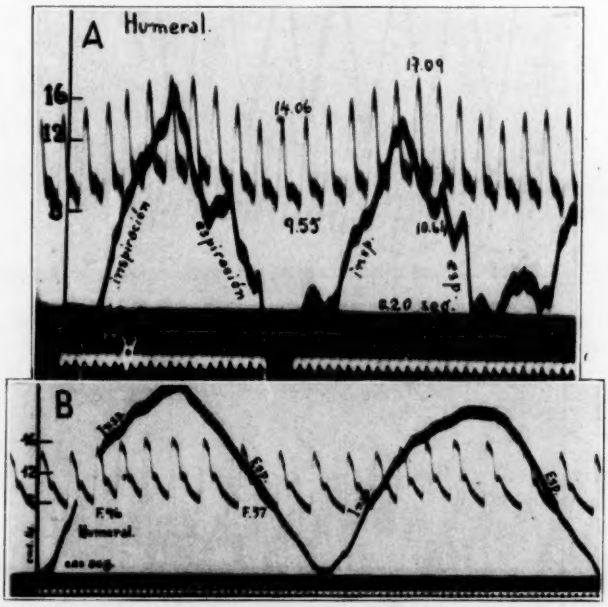


Fig. 3.—*A*, variations in the blood pressure during deep, slow thoracic breathing. This tracing shows a progressive rise in blood pressure (systolic and diastolic) during inspiration. The highest point is reached at the end of the inspiratory phase and the beginning of expiration. During expiration a fall of both pressures is seen. There are significant variations in pulse pressure. *B*, variations of blood pressure and cardiac rate during deep, slow thoracic breathing. A rise during inspiration, with tachycardia, and a drop during expiration, with bradycardia, are recorded.

was observed in 9, and a fall of the blood pressure during the same phase was noted in 3. The opposite occurred in inspiration; the rise of arterial pressure generally started at the beginning of expiration. The pulse pressure was increased with expiration in 6 subjects. In 10 an expiratory bradycardia was noted, and in the remainder there were no variations in the heart rate.

With deep breathing an expiratory increase was recorded in 8 tracings and an inspiratory rise in 2; in 7 the pulse pressure increased during expiration and in 2 during inspiration.

With deep thoracic breathing, an increase in pressure during expiration and a decrease during inspiration were recorded in 5 tracings. In 2 other tracings the pressure increased during inspiration; the pulse pressure rose during expiration in 4 and during inspiration in 1. Expiratory bradycardia was registered in 6.

In 2 cases we observed an inspiratory elevation during deep, slow abdominal breathing, with an increase in the pulse pressure in 1 case and in the other a fall; there was expiratory bradycardia in both. The rise began in 1 case in the middle and in the other at the very beginning of inspiration (the humeral artery

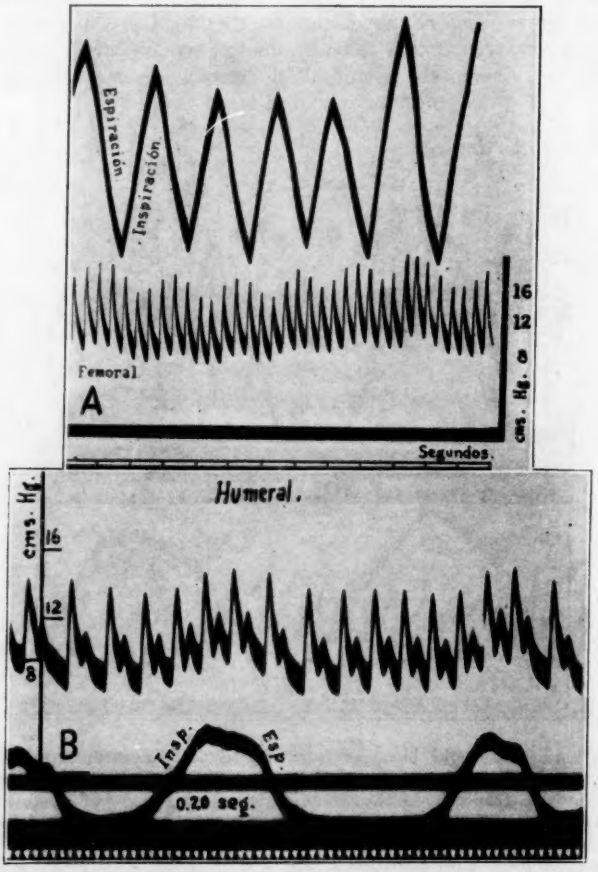


Fig. 4.—*A*, variations of blood pressure during deep, fast thoracic breathing. Blood pressure falls at the beginning of inspiration and rises at the end. *B*, variations of blood pressure during slow, deep abdominal breathing. This tracing shows a rise of the arterial pressure during inspiration and a fall during expiration. The fall in diastolic pressure and the consequent increase in pulse pressure are especially apparent.

was used for both). When without withdrawing the needle from the artery we told 1 of these patients to change the breathing from abdominal to thoracic, it was clearly registered that the blood pressure fell during inspiration.

In the same patients, when the rate of breathing was increased (by deep and fast abdominal movements), a fall of blood pressure during inspiration was

observed in 1, and in the other, even when the pressure rose on inspiration, the amplitude of the variations of arterial pressure diminished noticeably.

Among the many factors supposed to have a part in the production of respiratory waves, the changes which the intrapleural and the abdominal pressure undergo are worthy of consideration.

The negative pressure within the pleura is greater during inspiration than during expiration. During ordinary inspiration, a larger quantity of venous blood goes to the heart, because of the greater negative pressure within the thorax. At the same time, with the descent of the diaphragm, the abdominal pressure is increased. Both factors contribute to augment the inflow of blood to the heart at the end of inspiration. The result is an increase in the cardiac output in this phase.

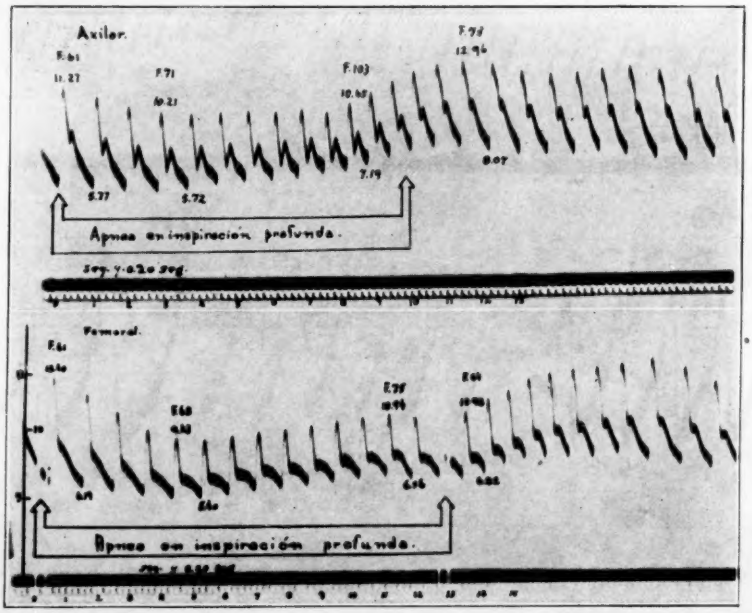


Fig. 5.—Inspiratory apnea. Variations in the blood pressure, in the shape of the pressure curve, in the pulse pressure and in the cardiac rate are clearly apparent. The decrease in pulse pressure and the exaggeration in the dicrotism are most evident.

During expiration, the phenomena are reversed, and there is a consequent diminution in the blood pressure.

We must still consider other factors, the intervention of which can alter the results stated above. We shall mention the anatomicophysiologic condition of the pulmonary bed, the variations in the diameter of the pulmonary blood vessels and the resistance which these vessels offer to the blood. The intrapericardial pressure is also significant.

During inspiration, especially at the beginning, the pulmonary bed admits a greater quantity of blood through expansion of the lung (Heinbecker[16] and

16. Heinbecker, P.: The Mechanism of the Respiratory Waves in Systemic Arterial Blood Pressure, Am. J. Physiol. **81**:170, 1927.

Trimby and Nicholson [17]). Consequently, the resistance to the blood in its pulmonary course and the inflow of blood to the left ventricle are lessened and the blood pressure tends to decrease.

In expiration, in spite of greater resistance of the pulmonary vessels, the blood flows more easily into the left auricle. The consequence of this is an increase in the systemic blood pressure. Furthermore, during inspiration there is a decrease in the intrapericardial pressure (Lewis [1]) with an increase in the diastolic inflow and the cardiac output.

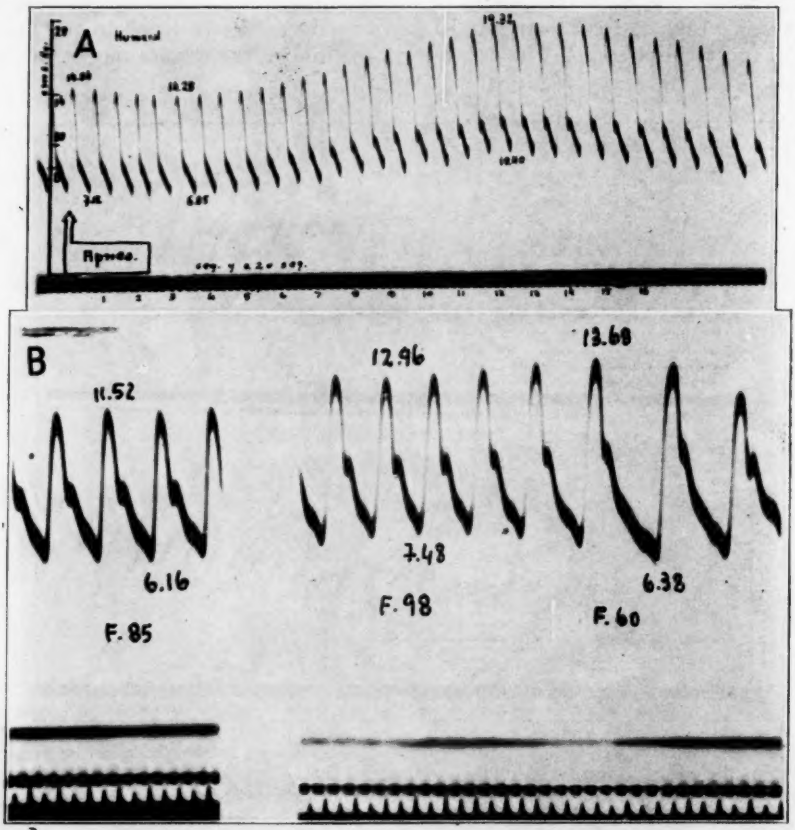


Fig. 6.—*A*, expiratory apnea. After a slight fall of pressure a continuous elevation of the systolic and the diastolic blood pressure and an increase of pulse pressure are noted. *B*, this tracing shows a rise of systolic and a fall of diastolic blood pressure, associated with an increase of the pulse pressure and bradycardia. The tracing was made at the time of the diaphragmatic and abdominal contractions which followed expiratory apnea.

The relationship between all these factors may explain the fluctuations of blood pressure in the course of normal breathing. In the following table we consider the different factors which act on the blood pressure.

With ordinary breathing there are generally, as we have stated, an inspiratory fall and an expiratory elevation of the blood pressure (fig. 2 *A*). The vascular

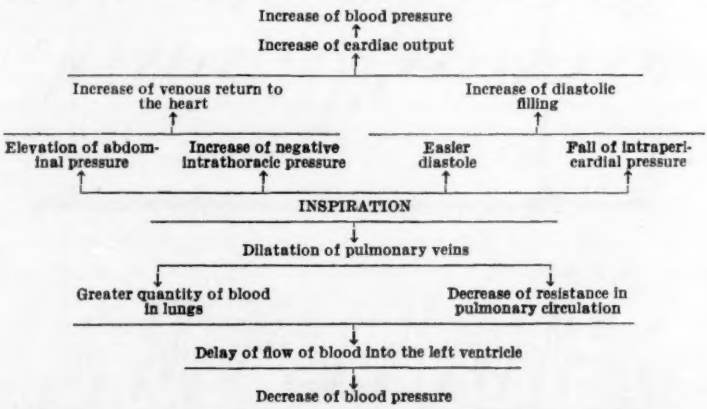
17. Trimby, R. H., and Nicholson, H. C.: Some Observations on the Nature of the Respiratory Waves in Arterial Blood Pressure, Am. J. Physiol. **129**:289, 1940.

capacity of the lung probably predominates over the thoracic-abdominal factor in these cases.

During deep, slow thoracic breathing, the variations of the blood pressure are clearer than during ordinary breathing. As has been previously stated, there are generally a fall in pulse rate and blood pressure during inspiration and a rise during expiration and the respiratory pause (fig. 2 *B*). The behavior of the blood pressure is neither constant nor uniform, as we have found cases in which it has risen during inspiration (fig. 3 *A*). These variations are independent of the heart rate. We generally found expiratory bradycardia (fig. 3 *B*), which commenced sometimes at the beginning and sometimes at the end of expiration and persisted during the respiratory pause.

An increase in blood pressure during inspiration is probably due to predominance of the factor of negative intrathoracic and positive abdominal pressure.

Factors Which Contribute to Variations of Blood Pressure During Inspiration


Increase of blood pressure
Increase of cardiac output
Increase of venous return to the heart
Increase of diastolic filling
Elevation of abdominal pressure
Increase of negative intrathoracic pressure
Easier diastole
Fall of intrapericardial pressure
INSPIRATION
Dilatation of pulmonary veins
Greater quantity of blood in lungs
Decrease of resistance in pulmonary circulation
Delay of flow of blood into the left ventricle
Decrease of blood pressure

This predominance favors the venous return to the heart and hence the systolic discharge of the ventricle. An increase in blood pressure during expiration leads one to suppose the predominance of the pulmonary factor, with a consequent increase in the venous return to the heart.

During deep, fast thoracic breathing an increase of the blood pressure during expiration was observed (fig. 4 *A*), and with deep, slow abdominal breathing there was a rise of blood pressure during inspiration (fig. 4 *B*).

Blood Pressure During Inspiratory Apnea.—The record of the arterial pressure curve during apnea following a deep inspiration shows that both the systolic and the diastolic pressure fall gradually in the first three to five seconds, and the dicrotism becomes more evident (fig. 5). The cardiac rate increases 6 or 7 beats per minute. The initial fall is followed by a gradual rise of the arterial curve and the cardiac rate until the end of the apnea. As soon as breathing is recommenced, the arterial curve regains its original state and the blood pressure returns to its original level, though during a few seconds it may be higher. These variations may even be recorded in arteries far from the thorax, e. g., in the posterior tibial artery.

The changes in the first seconds of the period of apnea may be explained on the basis of mechanical interference, chiefly blocking of the venous return to the heart, which tends to reduce the amount of blood flowing to the heart and produces diminution of the cardiac discharge.

The changes of the second phase may be explained by the intervention of reflex phenomena due to stimulation of vasomotor centers by the hypercapnemia or hypoxemia associated with any more or less prolonged respiratory pause.

Arterial Pressure During Expiratory Apnea.—In the course of the interval of apnea following an ordinary expiration, it is observed that after a slight decrease in blood pressure during the first seconds there is a progressive increase in the maximal, the medial and the minimal pressure until the end of the test, which

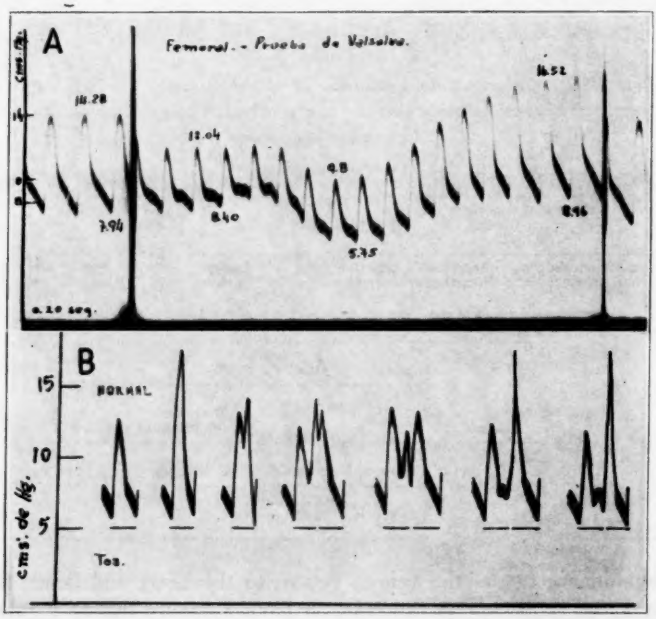


Fig. 7.—*A*, Valsalva test. Three phases are apparent. In the first two there is a definite fall of pulse and blood pressures. The fall in blood pressure is especially apparent in the second phase (empty pulse). In the third phase the pulse pressure definitely increases (full pulse). *B*, diagram showing the effects of the exertion of coughing on the intra-arterial pressure. Note the sudden rise of pressure caused by coughing and coincident with the different gradients of the pulse.

generally lasts from fourteen to twenty seconds. The pulse pressure also increases toward the end (fig. 6 *A*). Holding the breath for a longer period causes a series of muscular and diaphragmatic contractions with a terminal elevation of the arterial pressure and a slowing of the pulse (fig. 6 *B*).

The initial descent could be interpreted as the result of stopping the respiratory movements. The consequent elimination of the thoracic-diaphragmatic factor reduces the venous flow to the heart and diminishes the cardiac output. The subsequent rise could be explained by the excitation of the vasomotor centers caused by oxygen hyposaturation of the arterial blood (hypoxemia) or by accumulation of carbon dioxide (hypercapnemia). The cardiac rate increases slightly

as a result of the sympathetic stimulation. If the test is prolonged muscular contraction produces abrupt changes in intrathoracic pressure.

Valsalva Test.—The curves of the arterial pressure during the Valsalva test (expiratory effort with the glottis closed) show some similaritiy to those of inspiratory apnea. Three phases are noticeable (fig. 7 *A*):

1. The systolic pressure falls; the diastolic pressure rises, and a slight acceleration of the heart beat occurs. The pulse pressure diminishes, producing what is called by Hamilton and his associates "empty pulse." The decrease in the systolic pressure may be explained by the blocking of the venous return to the heart. The elevation of the diastolic pressure and the tachycardia may be due to a reflex originating in the carotid sinus (Hamilton, Woodbury and Harper [13]).

2. In the second phase there is a characteristic descent of both the systolic and the diastolic pressure. Hamilton and his associates, by measuring the intrathoracic and blood pressures simultaneously, have proved that during this phase the arterial pressure drops abruptly to the level known as "net" blood pressure. The value for the latter is obtained by subtracting the intrathoracic pressure from the arterial pressure.

3. When the strain is released, the pulse curve becomes characteristic of the type known as "full pulse"; the systolic and the diastolic pressure rise and surpass the level previous to the test and the cardiac rate becomes slower. These variations are interpreted as being caused by the abrupt flow of blood to the thorax and by reflexes originating in the cardioaortic region (Hamilton, Woodbury and Harper [13]).

Effect of Cough on Arterial Pressure.—The intra-arterial pressure was studied during the exertion of coughing, and it was found that it rose sometimes to very high levels. When the cough coincides with the top of the pulse curve, the systolic pressure may duplicate its normal values (fig. 7 *B*).

The influence which this phenomenon has on the cerebral arteries has been studied by Hamilton, Woodbury and Harper.[13] The simultaneous registration of intra-arterial, intrathoracic and intraspinal pressure has shown that an abrupt rise of intra-arterial pressure caused by coughing is accompanied by an increase in intraspinal pressure. Therefore, a rise in the intra-arterial pressure in the brain is accompanied by a correlative increase in the pressure of the cerebrospinal fluid, and possible rupture of an artery is avoided. They have proved that identical protecting mechanisms against abrupt rises in blood pressure exist in the thorax and in the abdomen.

SUMMARY AND CONCLUSIONS

The influence of breathing, inspiratory and expiratory apnea, the Valsalva test and coughing on the intra-arterial pressure in man was studied.

Two types of waves were found: (*a*) vasomotor waves, which are independent of the respiratory movements and should be called by the names of their discoverers, Traube and Hering, and (*b*) blood pressure waves depending on the respiratory movements (respiratory waves).

The different factors which influence the production of these waves have been commented on.

The intra-arterial pressure has no uniform or fixed behavior during the respiratory movements but may rise or fall in accordance with the type of breathing—thoracic or abdominal—or with the frequency or depth of respiration. Even

during ordinary breathing, slight changes are noticeable, the most constant being a fall of blood pressure during inspiration and an elevation during expiration. With deep, slow thoracic breathing there usually occur an inspiratory fall and an expiratory rise of the blood pressure. The opposite, as a rule, is true of abdominal breathing of the same type.

Curves of intra-arterial pressure registered during inspiratory apnea and the Valsalva test show a definite fall of blood pressure at the beginning, while those taken during expiratory apnea are characterized by a slight initial fall and a terminal rise. Coughing causes great increase in the blood pressure.

Professor Gonzalo Bosch and Dr. Enrique Mo Gatti gave us permission to conduct our investigations in the Hospicio de las Mercedes. Dr. Eduardo Braun-Menendez offered suggestions and criticisms.

Viamonte 1519.

RATE OF SEDIMENTATION OF ERYTHROCYTES IN SICKLE CELL ANEMIA

TRAVIS WINSOR, M.D., AND G. E. BURCH, M.D.
NEW ORLEANS

Since the original description of sickle cell anemia, by Herrick [1] in 1910, much has been written about this disease with little attention given to the problem of the sedimentation of the erythrocytes. A review of the literature since 1935 revealed 65 publications on sickle cell anemia. These articles contained 248 reports of cases, 149 being fairly detailed. In only 37 of these reports was the sedimentation rate mentioned. In 9 of the 37 the method used was not indicated, and in 24 there was no mention of the degree of anemia. Although these data are difficult to interpret, it would appear that in 7 instances the sedimentation rate was slow. Diggs [2] recorded the sedimentation rate in 27 of a series of 37 cases and found it to be slow in many instances. He noted a decided variation even in the same subject. No attempt was made to explain these findings. Bunting [3] in an in vitro study of the bloods of 4 patients with active sickle cell anemia and 1 with the "trait" found the sedimentation rate to be directly proportional to the degree of rouleau formation.

A review of the records of patients admitted (total, 287,257; Negro, 131,775) to Charity Hospital during the past five years (January 1937 to January 1942) showed 40 instances of active sickle cell anemia. In only 4 was the sedimentation rate recorded, and in all these it was slow. In addition, the relatively few data on the sedimentation rate reported before 1935 offer little information, since methods for its determination were not standardized at that time.

Because of the lack of information on the sedimentation rate in sickle cell anemia, the value of this procedure in clinical diagnosis and the frequency of sickle cell anemia in the Negro race (Diggs stated that it is the most commonly encountered primary blood dyscrasia in Negroes), a study was undertaken to evaluate some of the factors influencing the rate of sedimentation of the erythrocytes. An effort was made to standardize the procedure for cases of this disease in order that the previously reported variabilities of values might be controlled.

GENERAL METHOD OF STUDY

These observations comprise data collected in repeated studies of 15 patients with active sickle cell anemia and 14 controls. The subjects chosen as controls had blood pictures that varied from the normal to ones similar, except for sickling, to those encountered in the patients with sickle cell anemia. Six of them had anemia (due to various causes) other than sickle cell anemia. The 14 diseased control subjects had the following clinical states: diabetes mellitus, disseminated lupus erythematosus, benign hypertensive cardiac disease, tuberculous peritonitis, syphilitic heart disease, bleeding peptic ulcer and acute gastritis, pulmonary tuberculosis (2 subjects) and pernicious anemia (2 subjects). Three of the control subjects were normal. The details of the blood pictures of all of the patients with sickle cell anemia used in these studies are summarized in table 1. These patients were carefully studied in order to make certain that they were free from any complicating disease.

The blood was collected in a uniform manner as follows: The patient rested for fifteen minutes before the blood was drawn. A blood pressure cuff was used as a tourniquet and inflated to a pressure slightly above the diastolic. About 10 cc. of blood was removed from the antecubital vein, the entire procedure requiring not more than sixty seconds. Nine and five-tenths cubic centimeters of the blood was transferred immediately to a 10 cc. vial containing 8 mg. of dry potassium oxylate and 12 mg. of ammonium oxylate. The vial was immediately corked and gently rotated. The blood was placed in the sedimentation tubes within five minutes and the rate of settling measured by the method of Wintrobe.[4] When corrections for anemia were necessary the correction values of Wintrobe [4] were used. After this initial determination of the rate of sedimentation was completed, the volume of packed red cells was measured by centrifuging the hematocrit tube for thirty minutes at 3,000 revolutions per minute. Occasionally an additional ten minutes of centrifugation was done in order to make certain of complete packing, and in no instance was further packing noted.

In addition to these routine procedures, other groups of studies, to be described, were carried out to observe the influence of several factors on the rate of sedimentation.

From the Department of Medicine, School of Medicine, Tulane University, and Charity Hospital of Louisiana.

1. Herrick, J. B.: Peculiar Elongated and Sickle Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517-521 (Nov.) 1910.

2. Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695-700 (Feb. 25) 1939.

3. Bunting, H.: Sedimentation Rates of Sickled and Non-Sickled Cells from Patients with Sickle Cell Anemia, Am. J. M. Sc. **198**:191-193, 1939.

4. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**:102-114, 1935.

RELATION BETWEEN DEGREE OF ANEMIA AND SEDIMENTATION RATE

In order to learn the variations in the sedimentation rate with the degree of anemia in patients with sickle cell anemia, the bloods of 10 patients with active sickle cell anemia were observed, the sedimentation rates being determined as just outlined and the results correlated with the degree of anemia expressed as packed cell volume.

Results.—The sedimentation rates for the 10 patients, after correction by use of the Wintrobe chart, are summarized in figure 1. The 6 patients with the most severe anemia, all with packed cell volumes of less than 25 per cent, had rates which were slower than one would predict for the anemia. The 4 patients with less severe anemia, who had packed cell volumes greater than 25 per cent, had sedimentation rates which were within the expected range. The erythrocytes of 4 of the 6 patients with severe anemia did not settle the calculated normal distance even though they were allowed to remain undisturbed in the tubes for four days.

Comment.—These observations suggest that in sickle cell anemia factors exist which tend to retard the rate of sedimentation of the erythrocytes and may be related to the degree of anemia. Since all of the patients except patient 9 had a normochromic, normocytic anemia, it is unlikely that the slow settling is related to the volume of the erythrocytes or to the amount of hemoglobin packed into each one. Since the degree of sickling is more or less directly proportional to the degree of anemia, it is possible that the abnormal shape of the erythrocyte may influence the rate of sedimentation. This factor will be discussed later. No published data were encountered concerning effects of the blood serum on the sedimentation rate in sickle cell anemia. Although no attempts were made in these studies to evaluate this influence, or that of any of the chemical constituents of the serum, on the sedimentation rate, all reports encountered in the literature cited normal values for plasma proteins in patients with uncomplicated sickle cell anemia.[5] In 4 of 40 cases from Charity Hospital the values for total plasma proteins were normal. These constituents were not studied in the others. The blood cholesterol has been recorded in the literature as approximately normal in 6 patients.[6]

It is interesting that even when the erythrocytes were allowed to settle for as long as four days they did not fall the distance that they normally do in one hour. To our knowledge, this has not been described as associated with any other type of anemia. A persistently retarded sedimentation rate is sometimes seen in polycythemia vera and in severe dehydration. In these two states the erythrocytes are absolutely and relatively increased.

The results of this group of experiments indicate the lack of reliability of the Wintrobe correction chart for correcting for the degree of anemia in a patient with severe sickle cell anemia. Wintrobe [4] apparently did not test his correction chart with the bloods of persons with sickle cell anemia.

In order to study the effects of relative volumes of erythrocytes and serum on the sedimentation rate in sickle cell anemia, the next group of experiments was conducted.

TABLE 1.—*Details Concerning the Blood of the Fifteen Patients with Sickle Cell Anemia Used in the Experiments*

Subject No.	Sex	Age, Years	Red Blood Cell Count, Millions	White Blood Cell Count, Thousands	Hemoglobin (Newcomber), Gm. per 100 Cc.	Hematocrit Reading, %	Sedimentation Rate (Wintrobe), Mm. per Hr.	Mean Corpuscular Volume, Cubic Microns	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Hemoglobin Concentration, %	Differential Leukocyte Count, per Cent			
											P.	L.	M.	E.
1	F	8	3.13	11.4	9.6	29	29	92.6	30.6	33.1	67	22	6	4
2	F	8	2.2	35.0	6.6	20	23	90.9	30.0	33.0	85	12	3	0
3	M	16	1.9	10.2	...	14	24	93.3	....	....	70	25	4	1
4	M	23	...	....	9.0	31	41	....	....	30.6	..	..	..	..
5	M	15	2.7	12.8	6.5	25	5	92.5	24.0	26.0	59	25	3	2
6	F	23	2.3	18.9	7.3	21	40	91.3	31.7	34.7	73	22	5	0
7	M	37	1.4	6.9	...	16	45	....	....	....	49	54	2	0
8	M	7	2.7	14.0	7.3	19	15	70.3	27.0	38.4	68	21	8	3
9	M	18	2.8	27.7	7.0	21	17	75.0	25.0	33.3	66	27	5	1
10	F	13	2.8	12.6	7.8	27	2	96.4	27.8	28.8	50	32	3	1
11	F	26	2.5	8.4	9.3	21	1.5	98.2	37.2	28.5	51	34	5	8
12	F	5	3.8	25.7	10.0	35	36	92.1	26.3	26.3	..	..	..	..
13	F	38	...	....	...	38	10	....	....	....	..	..	..	..
14	M	14	2.1	21.0	0.5	19	6	90.4	30.9	30.9	..	..	..	..
15	F	7	2.3	24.0	7.2	21	7	91.3	31.3	34.2	70	22	5	3

5. Cooke, J., and Keller, M.: Sickle Cell Anemia in a White Family, J. Pediat. **5**:601-607, 1934.

6. Vryonius, G.: Studies of the Effect of Intravenous Administration of Liver Extract in Patients with Sickle Cell Anemia, J. Lab. & Clin. Med. **26**:1470-1473, 1941. Chediak, M.; Cabrera Calderín, J., and Prado y Vargas, G.: Sickle Cell Anemia in Cuba, Arch. de med. int. **5**: 313-370, 1939. Cabrera Calderín, J. G.; Labourdette Scull, J. M., and Prado y Vargas, G.: Dos casos de anemia a hematíes falciformes, Bol. Soc. cubana de pediat. **9**:179-206, 1937.

RELATION OF SEDIMENTATION TO VARIOUS DEGREES OF ANEMIA, ARTIFICIALLY PRODUCED

Four of the 10 patients used in the previous experiment were employed for these studies. Two were from the group of 6 with severe anemia and slow sedimentation rates, and the other 2 were from the group of 4 with moderate anemia and sedimentation rates that were within the expected range for the degree of anemia. The erythrocytes and plasma were separated and recombined in different proportions so that various degrees of artificial anemia were produced. The sedimentation rates were determined for each combination.

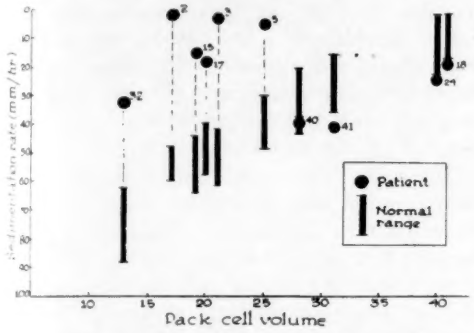


Fig. 1.—The relation between the degree of anemia and the sedimentation rates of 10 patients with sickle cell anemia.

Results.—The results are summarized in figure 2. It can be seen that the sedimentation rate increased as the artificially produced anemia increased. However, the sedimentation rate remained slower than that predicted from the Wintrobe chart, regardless of the degree of artificial anemia, in the patients with the severe anemia and relatively slow rates (fig. 2 *A*). In the patients with moderate anemia and sedimentation rates that were already within the expected range for this anemia, the erythrocyte sedimentation rate likewise remained within the calculated range regardless of the degree of anemia artificially produced (fig. 2 *B*).

Comment.—Artificially produced anemia will not produce a relative retardation of the sedimentation rate. In the first experiments it was found that in the cases of more severe anemia, with packed cell volumes of less than 25 per cent, the sedimentation rate was retarded out of proportion to the degree of anemia. In those studies only naturally occurring anemia was correlated with the sedimentation rate. In the latter group of studies the results indicate that it is not the degree of packed cell volume per se that is responsible for the retardation of the sedimentation, for when the anemia was varied artificially the sedimentation rate varied as would be expected from Wintrobe's correction charts. Therefore, it must be something else related to the degree of anemia, not the anemia per se, which tends to retard sedimentation. This suggests in vivo rather than in vitro phenomena. Since the sedimentation rate is not directly related to the concentration of the erythrocytes, it was then considered advisable to study the relationship of rouleau formation in sickle cell anemia and the sedimentation rate. It is appropriate for the sake of continuity of thought, to describe first observations on the effects of oxygen and carbon dioxide on sedimentation.

OXYGEN AND CARBON DIOXIDE AND THE SEDIMENTATION RATE

The effect of oxygen and carbon dioxide on the sedimentation rate was studied for 4 patients with sickle cell anemia and 4 control patients with conditions other than sickle cell anemia. Fifteen cubic centimeters of oxylated blood from each of the patients was divided into

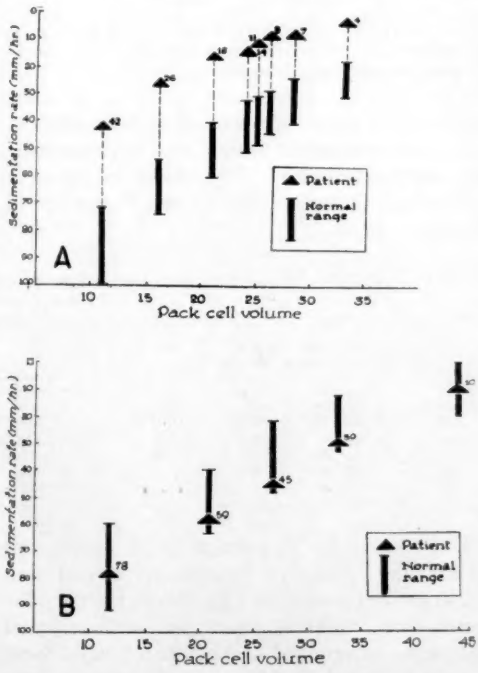


Fig. 2.—*A*, the effect of artificial anemia on the sedimentation rate of a patient in whom the degree of anemia was severe, the packed cell volume being less than 25 per cent. *B*, the effect of artificial anemia on the sedimentation rate of a patient in whom the degree of anemia was moderate, the packed cell volume being greater than 25 per cent.

three portions, each being placed in a 50 cc. Erlenmeyer flask containing air, approximately 100 per cent oxygen and approximately 100 per cent carbon dioxide, respectively. The sedimentation rate from the flask containing air was determined immediately. The remaining flasks

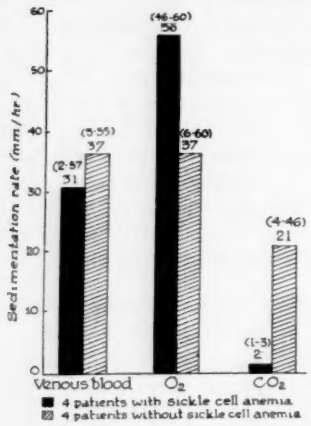


Fig. 3.—The effect of oxygen and carbon dioxide on the sedimentation rates of patients with sickle cell anemia and patients with other conditions.

were corked and were rotated occasionally for sixty minutes, after which the sedimentation rates were determined. The bloods of a patient with sickle cell anemia and a control were tested simultaneously.

hour. The effects in the control group were not nearly so marked.

The sedimentation rates of the bloods subjected to a negative pressure slightly greater than atmospheric, 780 mm. of mercury, for twenty-three minutes showed alterations similar to those produced by saturation with oxygen, although the bloods appeared grossly identical in color to those completely saturated with carbon dioxide (table 2). When the vacuum-treated blood was saturated with carbon dioxide, the sedimentation rate was reduced to almost zero, and when it was saturated with oxygen the rate was greatly accelerated.

Comment.—The mechanism by which carbon dioxide and oxygen produce the changes in sedimentation rate is unknown. Bunting [3] noted a similar effect and stated that oxygen tended to favor rouleau formation and decrease sickling while carbon dioxide had an opposite effect. Such morphologic changes were lacking in the control bloods. The relations of these phenomena are further discussed in the next group of experiments. Carbon dioxide has been known to increase the volume of the erythrocytes, inducing an exchange of electrolytes between the erythrocytes and the plasma, to change the p_H of the plasma and cells, etc.[7] The relative importance of these changes with regard to the sedimentation rate in normal and in diseased patients is not clear. The fact that the sedimentation rate

TABLE 2.—*Influence of a Vacuum on the Sedimentation Rates of Three Patients with Sickle Cell Anemia and Four Control Subjects*

Sickle Cell Anemia, Sedimentation Rate, Mm. per Hr.				Control Sedimentation Rate, Mm. per Hr.				
Venous Blood	Vacuum 23 Minutes, 780 Mm. Hg	Oxygen	Carbon Dioxide	Diagnosis	Venous Blood	Vacuum 23 Minutes, 780 Mm. Hg	Oxygen	Carbon Dioxide
31	35	63	1	Malnutrition	34	30	31	23
7	33	67	0	Pregnant, anemia	60	60	61	60
8	12	46	1	Normal	32	30	38	24
				Pyelitis	58	57	..	..

The bloods of 3 patients with sickle cell anemia and 4 control patients were subjected to a negative pressure of 780 mm. of mercury for twenty-three minutes, and the sedimentation rates were determined and compared with those previously found for the same bloods.

Results.—Oxygen invariably accelerated the sedimentation rates of the patients with sickle cell anemia, but did not accelerate the rates of the control patients. Carbon dioxide greatly retarded the sedimentation rates of the patients with sickle cell anemia and slightly retarded the settling rates of the control group (fig. 3). In fact, carbon dioxide almost entirely stopped the settling of the erythrocytes of the persons with sickle cell anemia, reducing it to 1 to 3 mm. in an hour. The effect was accelerated by the removal of oxygen, carbon dioxide and other gases by vacuum, an effect similar to that produced by saturation of the blood with oxygen, tends to indicate that it was the removal of the carbon dioxide that produced this effect. The blood had the dark color of reduced hemoglobin. An addition of oxygen further accelerated the rate of sedimentation, while an addition of carbon dioxide reduced the rate to almost zero. It is possible that addition of oxygen to the blood of persons with sickle cell anemia produces its effect by

7. Ham, H. T., and Curtis, F. C.: Sedimentation Rate of Erythrocytes, Medicine **17**:447-517, 1938. Fahraeus, R.: Suspension Stability of the Blood, Physiol. Rev. **9**:241-274, 1929.

decreasing the relative amounts of carbon dioxide.

ROULEAU FORMATION AND THE SEDIMENTATION RATE

The relationship of rouleau formation and the sedimentation rate was studied in 5 patients with severe sickle cell anemia. Five patients with conditions other than sickle cell anemia were used as control subjects. Immediately after the blood had been collected as previously described, a drop was placed on a slide under a cover slip and sealed in with petrolatum. About 5 cc. of the remaining blood was placed in each of two 50 cc. Erlenmeyer flasks. One flask was already filled with oxygen and the other with carbon dioxide. Each was rotated occasionally over a period of about sixty minutes in order to insure saturation of the contained blood with the respective gases. A wet preparation was made with a drop from each of the flasks, as previously described for the venous blood, and rouleau formation was observed. At the time each of the preparations was made for study of rouleau formation, a preparation for determination of the sedimentation rate was set up and the rate determined.

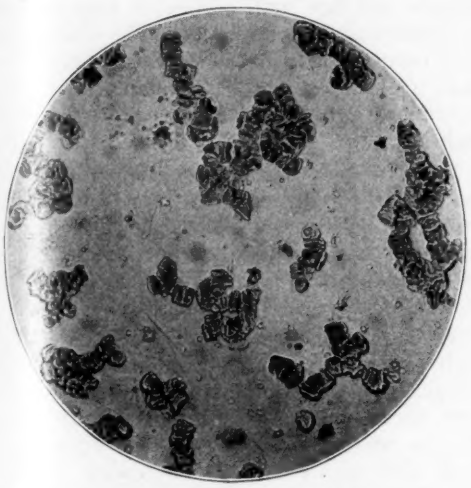


Fig. 4.—Rouleaux as seen immediately after removal of venous blood from the antecubital vein. These were of an "abnormal" character and resembled agglutination because of the more or less haphazard clumping.

Results.—In the bloods of the 5 control patients normal rouleau formation was seen. On the other hand, the bloods from the patients with sickle cell anemia showed at least three different types of phenomena, depending on whether or not they were saturated with oxygen or carbon dioxide or were merely venous blood:

1. The erythrocytes of venous blood congregated to form rouleaux of an "abnormal" type. These rouleaux were imperfect in that the erythrocytes were not stacked neatly but were gathered in irregular masses resembling agglutination rather than rouleaux (fig. 4). Pressure on the cover slip dispersed the rouleaux and separated the cells momentarily. After three to five minutes the cells reunited in their "abnormal" formation. When the erythrocytes were dispersed they showed signs of early sickling.

2. The blood that was saturated with carbon dioxide showed no evidence of rouleau formation, not even a tendency of the erythrocytes to aggregate. There was marked sickling (fig. 5).

3. The blood saturated with oxygen showed rouleau formation that appeared to be normal in every respect (fig. 6).

The rate of sedimentation showed a definite correlation with rouleau formation (fig. 7). The venous blood which showed the "abnormal" rouleaux had a mean sedimentation rate of 21 mm. in one hour. The blood saturated with carbon dioxide, which showed no rouleaux, had an average rate of 2 mm. while the blood saturated with oxygen, which showed normal rouleaux, had a rate of 48 mm. Corrections were made for the degree of anemia.

Fig. 5.—Absence of rouleaux after saturation of the blood with carbon dioxide. Sickling is about 100 per cent.

Comment.—Since it is well known that the rate of sedimentation is directly proportioned to the degree of rouleau formation, these results are not surprising.[8] The extent to which carbon dioxide and oxygen influenced these phenomena,

8. Cutler, J. W.; Park, F. R., and Herr, B. S.: The Influence of Anemia on Blood Sedimentation, Am. J. M. Sc. **195**:734-751, 1938.

however, is interesting. In active sickle cell anemia the rouleaux are imperfect. They can be made normal by saturation with oxygen and made to disappear completely with carbon dioxide. The mechanism of the action of these gases is unknown; whether it is the carbon

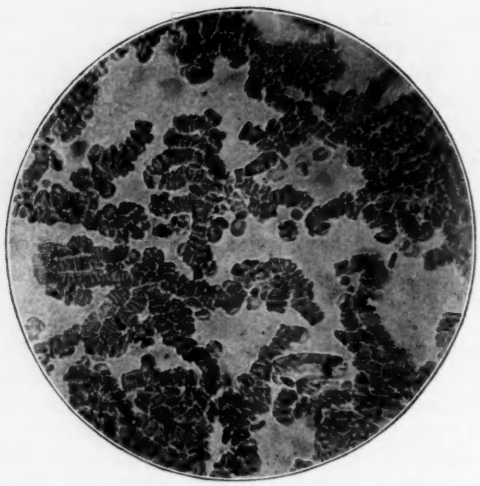


Fig. 6.—"Normal" rouleau formation after saturation of the blood with oxygen.

dioxide or the lack of oxygen that is important has not been definitely determined. The studies with a negative pressure tend to indicate that it is the presence of carbon dioxide that is important. This will be discussed further. These gases might ultimately produce their effects by changing the structure of the erythrocytes, for it has been shown that sickling is increased by carbon dioxide and decreased by oxygen. It would seem to be difficult to stack sickled cells neatly in rouleaux. Of course, there are many other conceivable possibilities that could explain these findings. In many instances, blood saturated or partly saturated with carbon dioxide showed an "abnormal" type of rouleaux when viewed immediately on removal from the flask. The sedimentation rates of these bloods were slow, although free sickle cells were not yet in abundance. When free sickle cells were in abundance the sedimentation rate was invariably slow. This suggests that there are other factors beside the type of rouleaux which affect the sedimentation rate after gaseous saturation, although the type of rouleaux seems to be of great importance.

As will be shown in the next group of experiments, the sickling, rouleau formation and slow sedimentation rate are reversible. Fluctuations from one state to the other can be made to take place with the use of oxygen and carbon dioxide.

REVERSIBILITY OF THE SEDIMENTATION RATE

The reversibility of the sedimentation rate was studied in 5 patients with sickle cell anemia and 3 patients with disease states other than sickle cell anemia. A sample of blood of each of the patients was collected and saturated with carbon dioxide and then with oxygen or with oxygen and then with carbon dioxide. The saturations were carried out in Erlenmeyer flasks as previously described. The sedimentation rate was determined after the blood was saturated with each gas.

Results.—The results are graphically summarized in part by figure 8. As found in the group of experiments immediately preceding, carbon dioxide greatly retarded sedimentation of the erythrocytes of blood showing sickle cell anemia and oxygen accelerated it.

When the sedimentation rate was retarded by carbon dioxide, saturation of the blood with oxygen would accelerate the rate of sedimentation, increasing it to what it was when only oxygen was used, making it even more rapid than that for venous blood alone. Carbon dioxide would retard sedimentation of erythrocytes of blood previously accelerated with oxygen. The marked quantitative changes produced by these gases may be noted in figure 8. No attempt was made to learn the number of times the rate could be reversed by serially alternating the saturations of the blood with oxygen and carbon dioxide, although the

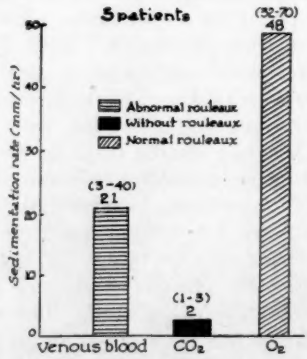


Fig. 7.—The relation between the type of rouleau formed and the sedimentation rate.

sedimentation rate was reversed in 2 patients when oxygen, carbon dioxide, oxygen, and carbon dioxide were used consecutively.

The sedimentation rates of the erythrocytes of the control group of subjects were also changed, but these changes varied qualitatively as well as quantitatively, the changes never being

as dramatic as with sickle cell anemia and, in some cases, not even being reversible (fig. 8 *A*).

Comment.—These findings are in keeping with those found in the preceding study and similarly show a correlation with rouleaux and sickling. The fact that the sedimentation rate

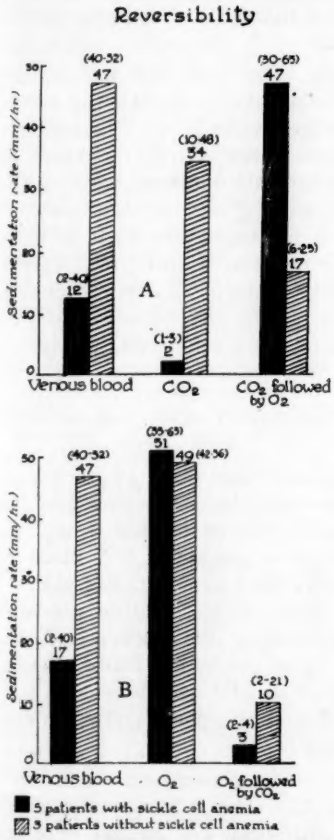


Fig. 8.—The effect of the successive saturation of a single sample of blood of patients with and without sickle cell anemia (*A*) with oxygen and then with carbon dioxide and (*B*) with carbon dioxide and then with oxygen.

of the blood of the patients with sickle cell anemia was reversible and that of the controls was not reversible (fig. 8 *A*) suggests an interesting qualitative difference between blood of persons with sickle cell anemia and with other types of disease. This qualitative difference was not noted when oxygen was administered first (fig. 8 *B*). It is necessary that a much larger number of bloods from patients with many types of disease states be studied before the significance of these findings can be evaluated.

Saturation of the blood with carbon dioxide increased its packed cell volume, the increase being as great as 12 per cent. This is in keeping with studies of Smirk,[9] who found increases of cell volume as great as 17 per cent after saturation of blood with carbon dioxide.

It was noted in freshly drawn venous blood that the degree of sickling was less among the cells taken from the upper part of the erythrocyte layer in the Wintrobe tube and greater among cells taken from the bottom. It is possible that there is greater anoxia among the latter group of cells. Theoretically, therefore, the cells at the bottom would tend to fall more slowly and impede the fall of the more rapidly settling and better oxygenated erythrocytes near the top of the erythrocyte column.

EXPOSURE OF BLOOD TO AIR AND THE SEDIMENTATION RATE

The effect of blood's standing in air on the sedimentation rate was studied in 3 patients with sickle cell anemia and 3 patients with other clinical states. Five cubic centimeters of blood from each patient was allowed to stand in a 50 cc. Erlenmeyer flask for sixty minutes. The flask was rotated for one minute out of every fifteen. Sedimentation rates were determined before and after exposure to air.

Results.—The sedimentation rate of the blood of patients with sickle cell anemia was increased to approximately three and one-half times the sedimentation rate determined immediately after the blood was drawn from the vein. The sedimentation rate of the control bloods was unchanged (figs. 9 *A* and 10).

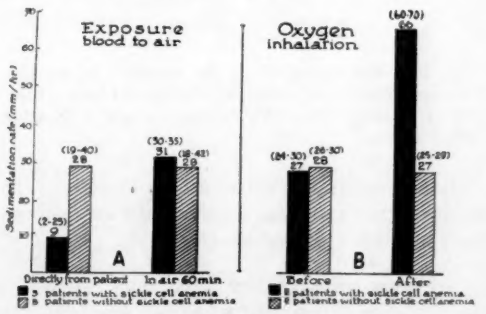


Fig. 9.—*A*, the sedimentation rate before and after exposure of blood to air for sixty minutes. *B*, the sedimentation rate before and after inhalation of 100 per cent oxygen for twenty-three minutes.

Comment.—The acceleration of the sedimentation rate of blood exposed to air in patients with sickle cell anemia is similar to that seen when the blood of such patients is saturated with oxygen. In the experiments in which blood was saturated

9. Smirk, H. F.: The Accurate Measurement of the Proportion of Corpuscles and Serum in Blood, Brit. J. Exper. Path. **9**:81-89, 1928.

with 100 per cent oxygen the sedimentation rate was twice the sedimentation rate of blood taken directly from patients. The increase in the settling rate of blood standing in air (about 20 per cent oxygen) was of the same order of magnitude as that seen when 100 per cent oxygen was used.

The state of previous gaseous saturation of the blood is probably important in determining the degree of acceleration of the sedimentation rate when blood stands in air. Cardiac disease, pulmonary disease or muscular exertion contributes to anoxia and an accumulation of carbon dioxide. If blood from such patients is allowed to stand in air and become oxygenated, a greater acceleration of sedimentation rate may result than if the blood were not initially anoxic. This situation may be comparable to the in vitro acceleration by oxygen of the sedimentation rate of blood

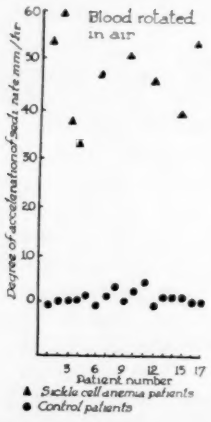


Fig. 10.—The degree of change produced by aeration of venous blood in the sedimentation rates of the erythrocytes of patients with sickle cell anemia and with other clinical states.

previously saturated with carbon dioxide. The sedimentation rate was accelerated twenty-three times by such a procedure (fig. 8 *A*).

OXYGEN INHALATION AND THE SEDIMENTATION RATE

In the previous studies the effects of oxygen were observed in vitro. In order to observe its effects in vivo on the sedimentation rate, 2 subjects with sickle cell anemia and 2 subjects with an anemia other than the sickle cell type were made to breathe 100 per cent oxygen for twenty-three minutes in a clinical Benedict-Roth basal metabolism apparatus. The exhaled carbon dioxide was removed with soda lime. The sedimentation rate of the erythrocytes of each subject was measured before and after the breathing of oxygen.

Results.—The results are summarized in figure 9 *B*. The sedimentation rates of the erythrocytes of the patients with sickle cell anemia were accelerated in vivo, as well as in vitro, while the sedimentation rates of the other subjects were not affected. The sedimentation rates of the subjects with sickle cell anemia were more than doubled by the inhalation of oxygen.

Comment.—The fact that the sedimentation rates of the patients with sickle cell anemia were so greatly accelerated by their breathing 100 per cent oxygen indicates that the blood of these patients is not fully saturated with oxygen when they are breathing air. It also shows the need for controlling oxygen saturation of the blood of these patients when studying their erythrocytes.

The effect of oxygen on several phases of the blood other than the sedimentation rate for patients with sickle cell anemia has been studied by others.[10]

THE TOURNIQUET AND THE SEDIMENTATION RATE

The sedimentation rate was determined for 4 patients with sickle cell anemia and 4 patients with other disease states before and after the application of a tourniquet. A blood pressure cuff, used as the tourniquet, was placed around the arm of each subject, and the pressure in the cuff was increased to a level just above the diastolic blood pressure. Blood was collected from the antecubital vein below the tourniquet at the end of sixty seconds and again at the end of ten minutes.

Results.—The results are shown in figures 11 *A* and 12. The sedimentation rates of the subjects with sickle cell anemia were markedly decreased, while those of the other subjects were not changed. The sedimentation rate of 1 of the patients with sickle cell anemia was only 5 mm. in one hour initially and was reduced to 2 mm. by the tourniquet. Application of the tourniquet produced an increase in the packed cell volume of both groups of subjects.

10. (*a*) Reinhard, E. H.; Moore, C. V.; Dubach, R., and Wade, L. J.: The Effect of Breathing 80% to 100% Oxygen on the Erythrocyte Equilibrium in Patients with Sickle Cell Anemia, Proc. Central Soc. Clin. Research **15**:13-14, 1942. (*b*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia, Arch. Int. Med. **39**:233-254 (Feb.) 1927. (*c*) Schriver, J. B., and Waugh, T. R.: Studies on a Case of Sickle Cell Anemia, Am. J. M. Sc. **181**:134, 1931; abstracted, Canad. M. A. J. **13**:375, 1930. (*d*) Klinefelter, H. F.: The Heart in Sickle Cell Anemia, Am. J. M. Sc. **203**: 34-51, 1942. (*e*) Sherman, I. J.: The Sickling Phenomenon with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, Bull. Johns Hopkins Hosp. **67**:309-324, 1940.

Comment.—The results of this group of experiments were to be expected in view of the previous in vitro studies of the effects of saturation of the blood with carbon dioxide. A venous stasis as produced by the tourniquet results in a decrease of the oxygen content and an increase of the carbon dioxide content of the venous blood. One subject with sickle cell anemia had an initial sedimentation rate of 5 mm. in one hour and this rate was decreased to 2 mm. by venous stasis, a decrease of 3 mm., or a change of 60 per cent. The initial rate was so slow that one would not expect as great a reduction as in a subject whose initial rate was much more rapid, e. g. 30 mm. or more in an hour.

Furthermore, these results show the extreme importance of controlling the length of time the tourniquet is applied when one is collecting blood for study in patients with sickle cell anemia. A great part of the change produced by the tourniquet must be due to the gaseous changes that result, but hemoconcentration, with

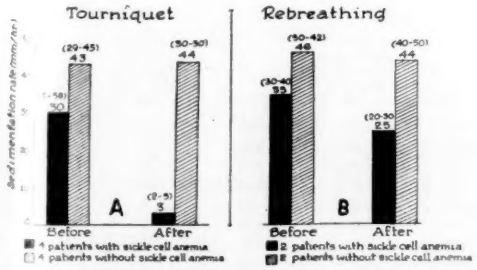


Fig. 11.—*A*, the sedimentation rate before and after the application of a tourniquet for ten minutes. *B*, the sedimentation rate before and after rebreathing into a bag.

an increase in the plasma protein, concentration of the cellular elements and the like, probably plays an important role.

EFFECTS OF REBREATHING ON THE SEDIMENTATION RATE

This group of experiments, like the preceding two, were in vivo studies. The sedimentation rates of 2 patients with sickle cell anemia and 2 with other disease states were determined before and after each rebreathed into a bag. They were allowed to breathe into the bag for two minutes, or until they showed symptoms of carbon dioxide accumulation.

Results.—The sedimentation rates of the 2 patients with sickle cell anemia were slowed 40 per cent, whereas there was no significant slowing of the rates of the other 2 patients (fig. 11 *B*).

Comment.—The effect of rebreathing is similar to that produced by application of a tourniquet or by saturation of the blood in vitro with carbon dioxide. These results indicate the importance of controlling the systemic accumulation of carbon dioxide generally when studying the blood of patients with sickle cell anemia.

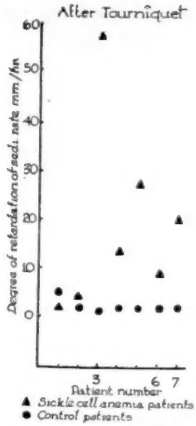


Fig. 12.—The degree of retardation by the application of a tourniquet of the sedimentation rates of the erythrocytes of patients with sickle cell anemia and with other clinical states.

CORRELATION OF INFLUENCE OF OXYGEN, AIR AND CARBON DIOXIDE AND OF THE TOURNIQUET ON THE SEDIMENTATION RATE

Figure 13 illustrates, on the one hand, the similarity of the effects of saturation of blood with oxygen and with air in accelerating the sedimentation rate of the erythrocytes of persons

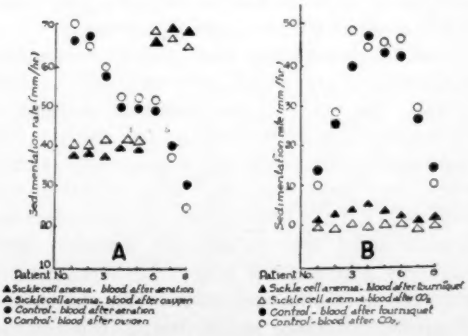

A
B
Patient No.
Sickle cell anemia - blood after aeration
Sickle cell anemia - blood after oxygen
Control - blood after aeration
Control - blood after oxygen
Sickle cell anemia - blood after tourniquet
Sickle cell anemia blood after CO2
Control - blood after tourniquet
Control - blood after CO2

Fig. 13.—*A*, the close relation between the degree of acceleration of the sedimentation rate produced by aeration and by oxygenation of venous blood from patients with sickle cell anemia and with other clinical states. *B*, the close relation between the degree of retardation of the sedimentation rate produced by application of a tourniquet and by saturation of venous blood with carbon dioxide.

with sickle cell anemia and, on the other hand, the similarity of saturation of blood with carbon

dioxide by means of the pure gas and by venous stasis (tourniquet). These figures also show the lack of such changes in the bloods of patients with clinical states other than sickle cell anemia.

CORRELATION OF THE p_H OF WHOLE BLOOD AND THE SEDIMENTATION RATE

Table 3 shows the relation of the p_H of whole blood to the sedimentation rate of the blood of 4 patients with sickle cell anemia and 4 patients with other clinical states. Two of the latter had anemia. Separate samples of blood from each patient were saturated with oxygen, air and carbon dioxide, and the p_H was determined potentiometrically with a p_H meter accurate to 0.01 p_H. The double oxylate solution already described was used as the anticoagulant, except for the blood of patients 7 and 8 of table 3. Ten milligrams of potassium oxylate for each 6 cc. of blood was used for these 2 patients.

The blood saturated with oxygen or air was alkaline, and the blood saturated with carbon dioxide was acid. The sedimentation rates of the erythrocytes both of the control subjects and of patients with sickle cell anemia were slower when the blood was acid than when it was alkaline. For the latter group the sedimentation rates in acid and in alkaline mediums were markedly different, the range of difference being from 39 to 56 mm. per hour. For the control group the difference varied from 2 to 5 mm. per hour. The p_H values for the patients with sickle cell anemia and the control subjects were not significantly different.

Comment.—The changes in p_H brought on by the saturation of the blood samples with oxygen or carbon dioxide were expected. The next experiment was conducted in order to learn whether or not the changes in sedimentation were related to the p_H of the blood.

ALTERATION OF THE p_H BY MEANS OF OXALIC ACID AND ITS EFFECT ON THE SEDIMENTATION RATE

Five cubic centimeters of blood from patients 5 and 6 (table 3) were saturated with air. Crystals of oxalic acid were added until the p_H approached that found when the bloods were saturated with carbon dioxide. Sedimentation rates were then determined. The results are shown in table 4.

The sedimentation rates were altered only slightly by this procedure. Patient 5 had a sedimentation rate of 38 mm. per hour in air when the p_H was 7.69, and after acidification with oxalic acid to a p_H of 6.02 the sedimentation rate became 45 mm. per hour. Patient 6 had a sedimentation rate of 41 mm. per hour after aeration (p_H 7.68). After acidification to a p_H of 6.32 with oxalic acid, the sedimentation rate was 36 mm. per hour.

Comment.—From these experiments it would seem that it is not the changes in p_H produced by carbon dioxide or oxygen that are responsible for the effects on sedimentation produced by these gases. These gases must produce their influence through some other mechanism than the mediation of p_H.

TABLE 3.—*Relation Between the Sedimentation Rate, the p_H of Whole Blood and Saturation of the Blood with O_2, Air and CO_2 for Four Patients with Sickle Cell Anemia and Four Patients with Other Conditions*

Patient No.	Diagnosis	Oxygen		Air		Carbon Dioxide	
		Sedimentation Rate, Mm. per Hr.	p_H	Sedimentation Rate, Mm. per Hr.	p_H	Sedimentation Rate, Mm. per Hr.	p_H
1	Ulcerative colitis	24	7.62	22	7.62	19	6.40
2	Gout	47	7.66	46	7.61	42	6.45
3	Bleeding peptic ulcer	21	7.68	20	7.61	19	6.47
4	Bleeding peptic ulcer	52	7.78	50	7.63	50	6.43
6	Sickle cell anemia	40	7.71	39	7.69	1	6.42
5	Sickle cell anemia	45	7.64	41	7.68	1	6.32
7	Sickle cell anemia	57	8.25	63	8.10	1	6.69
8	Sickle cell anemia	43	8.28	50	8.12	1	6.78

* The p_H values were the values found for the whole blood after saturation with the respective gases.

TABLE 4.—*The Relationship Between the Sedimentation Rate of the Erythrocytes and the p_H of Whole Blood of Two Subjects with Sickle Cell Anemia* *

Patient No.	Aeration		Acidification with Oxalic Acid	
	Sedimentation Rate	p_H	Sedimentation Rate	p_H
5 (table 3)	39	7.69	45	6.02
6 (table 3)	41	7.68	36	6.32

* The bloods were first aerated and then the p_H and sedimentation rates measured. The oxalic acid crystals were then added very slowly in order to reduce the p_H to about the level produced by saturation with carbon dioxide (table 3), and then the sedimentation rate was measured again.

GENERAL COMMENT

The experiments described illustrate some of the factors which may alter the sedimentation rate of the blood of patients with sickle cell anemia. Inhalation of oxygen, exposure of blood to air and oxygenation of blood in vitro accelerate the sedimentation rate. Rebreathing into a bag, application of a tourniquet and saturation of blood with carbon dioxide in vitro all retard the sedimentation rate. These changes occur independently of the p_H and at least depend on the degree of carbon dioxide saturation of the blood.

Oxygen restores sickled cells to the discoid form, fosters normal rouleau formation and restores the sedimentation rate to about the expected rate for the degree of anemia. This supports the value of oxygen therapy in the acute crisis of sickle cell anemia. However, Reinhard [10a] administered 100 per cent oxygen by means of an oxygen mask continuously for from eight to twenty days and noted a fall in the reticulocyte and the erythrocyte count. He interpreted this to indicate a depression of erythropoiesis. There is a need for further studies of this nature. In spite of these findings, it may be advisable to administer a proper concentration of oxygen to patients with severe active sickle cell anemia in the hope that the oxygen will restore the circulating erythrocytes to a more normal state.

When operation is necessary for these patients, an anesthetic gas which does not produce anoxemia is probably preferable. Correct choice of the anesthetist is as important as the choice of the anesthetic agent. Avoidance of anoxemia by proper technic may favor a successful outcome of a surgical procedure. The effect of anesthetic gases on the blood of patients with sickle cell anemia has not been studied, to our knowledge. It would seem, however, that gases requiring a minimum of oxygen to produce satisfactory anesthesia, such as nitrous oxide, would be contraindicated, whereas gases which allow full oxygenation of the blood during anesthesia, such as ether, would be preferable.

A changing sedimentation rate in the same patient from day to day has been mentioned.[2] This may be due to changes in the disease state of the patient or in other physiologic states which vary normally, such as the oxygen and the carbon dioxide content of the blood. It has been shown that these gases may influence greatly the sedimentation rate. It is also likely that the inconstancy of results reported by others is due to variations of technic employed in the collection of the blood or in the handling of the blood once it was collected. It has been shown in these studies that the duration of application of a tourniquet has a marked effect on the sedimentation rate. This is also true of the length of time the blood is exposed to air. It is likewise possible that the sedimentation rate is slower for venous blood than for arterial blood.

Equal degrees of change in p_H produced either by carbon dioxide saturation of whole blood or by addition of oxalic acid to the blood did not result in similar effects on the sedimentation rates of the erythrocytes of persons with sickle cell anemia. Carbon dioxide delayed sedimentation, while oxalic acid had no effect. In the control groups, an equal p_H change produced either by carbon dioxide or by oxalic acid had no significant effect on the sedimentation rate of the erythrocytes. These findings suggest that carbon dioxide per se and not necessarily the change in p_H produced by the carbon dioxide is the significant factor that so markedly influences sedimentation.

It is not difficult to understand how simple it is to find variable results in the sedimentation rate of the blood of persons with sickle cell anemia when so many factors produce such great changes. These observations indicate the need for controlling rigidly the method employed when comparing data for a single patient or for different patients. In view of the many factors affecting the sedimentation rate, it is difficult to interpret the sedimentation rates recorded in the literature, especially when the methods used were not carefully controlled or described in detail. In order to standardize more the methods used in studying the blood of patients with sickle cell anemia, the following suggestions are made:

1. The patient should be examined for evidence of pulmonary or cardiac disease or any other state which tends to produce anoxia, so that the degree of anoxemia can be estimated.

2. He should rest for fifteen minutes before blood is drawn, so that his blood will reach a state of chemical equilibrium.

3. A tourniquet should be allowed to remain on the arm for not longer than sixty seconds during the withdrawal of the blood, and the technic should be constant when patients are compared.

4. A quantity of blood should be drawn which will almost fill the vial into which it is to be placed, since this prevents excessive oxygenation of the blood. The vial should be corked immediately and rotated only sufficiently to insure mixing of the blood and the anticoagulant.

5. A dry anticoagulant should be used, so as not to introduce gases contained in a fluid anticoagulant.

6. The sedimentation rate should be determined immediately, at a fairly constant temperature.

It is well to point out again that the degree of change in the sedimentation rate produced by factors which influence sedimentation, such as oxygen, carbon dioxide and air, depends to a great extent on the initial rate of sedimentation. All factors being equal, oxygen will produce a greater acceleration of sedimentation if the initial value is low and carbon dioxide will produce a greater deceleration if the initial rate is rapid, and vice versa. For such reasons, it is difficult to compare or to evaluate the amount of change, and it is therefore better to compare levels reached when the sedimentation rate is changed. The application of these principles to the diagnosis of sickle cell anemia will be considered in a subsequent report.

SUMMARY

Several groups of experiments demonstrate some of the factors which influence the sedimentation rate of the erythrocytes of patients with sickle cell anemia.

The sedimentation rates of 6 of 10 patients with sickle cell anemia were slow when compared with their packed cell volumes. The patients with the most severe anemia had the slowest sedimentation rates.

Additional anemia produced artificially in the blood of patients who already had mild or severe anemia did not produce a comparable slowing of the sedimentation rate. It is therefore not the anemia itself which produces the slow sedimentation rate, but some other factor which changes concomitantly with the decrease in erythrocytes.

The data indicate strongly that it is carbon dioxide per se and not the change in p_H produced by carbon dioxide that so significantly slows the rate of sedimentation of the erythrocytes.

The sedimentation can usually be correlated with the type of rouleau formation, being rapid when rouleaux are "normal," somewhat slow when they are "abnormal" and very slow when they are absent. Although the sedimentation rate was invariably slow when rouleau formation was absent, the slow rates seen when rouleaux were abnormal suggests that other factors besides the formation of rouleaux affect the sedimentation rate.

The sedimentation rate of blood saturated with oxygen was invariably accelerated, and the sedimentation rate of blood saturated with carbon dioxide was invariably retarded. The retardation was frequently so great that severely anemic blood did not settle more than 2 or 3 mm. in four or five days.

The sedimentation rate is accelerated by placing blood in a vacuum of 780 mm. of mercury for twenty-three minutes. Carbon dioxide probably greatly retards the sedimentation rate by mechanisms other than mere exclusion of oxygen.

The sedimentation rates of patients with sickle cell anemia could be slowed or accelerated by alternate saturation with carbon dioxide and oxygen; that is, the sedimentation rates were reversible and varied considerably. Normal blood was affected only slightly by these gases.

Inhalation of pure oxygen accelerated the sedimentation rate, as did also exposure of the blood to air.

Keeping a tourniquet on the arm for ten minutes retarded the sedimentation rate, as did also rebreathing into a paper bag.

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Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1942 TO JULY 1943

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A review of the literature regarding physiology and disease of the digestive tract is of particular interest at the present time. Gastrointestinal disease and disturbances of gastrointestinal function constitute one of the most important medical problems of the war, affecting both the armed forces and civilians. Because of this fact, the present review will include mention of many articles that do not contain strictly new material but which may call attention to the numerous factors influencing the behavior of the alimentary tract.

PHYSIOLOGIC ASPECTS

Perusal of the literature on this subject reveals more than ever the multiplicity of factors entering into properly integrated gastrointestinal function. Many of these factors are still little understood or purely hypothetic, but on the whole a much clearer understanding is apparent of the relationship between the nervous system, the glands of internal secretion and gastrointestinal function.

Motor Aspects.—An excellent general discussion of digestion and the nervous system is that of Thomas,[1] who outlines first the extrinsic innervation of the stomach and of the small and the large bowel. He discusses the effects of vagotomy and sympathectomy on the motor activity of the various levels of the digestive tract. Thus the immediate effect of vagotomy is pronounced loss of tonus and motility in the fasting stomach, whereas section of the splanchnic nerves has less effect on gastric motility than division of the vagi. In the small bowel parasympathetic denervation has apparently only minor effects on the activity of the smooth muscle, but stimulation of the sympathetic nerves, as a rule, results in loss of tone and cessation of motility. Stimulation of the parasympathetic innervation of the large intestine via the pelvic nerves appears to augment the activity of both the circular and the longitudinal muscles of the large intestine and at the same time to cause relaxation of the internal anal sphincter. Removal of the inferior mesenteric ganglion in dogs causes a persistent diarrhea. The predominant action of the sympathetic innervation of the large bowel appears to be largely inhibitory. Thomas also discusses the innervation of the digestive glands and central mechanisms. He refers particularly to the recent studies by Wolf and Wolff in relation to the effects of emotional disturbances. As an informative and enlightening presentation of the factors influencing gastric function, the reviewer would like to give particular credit to the experimental studies of these two investigators.[2] Their most important

1. Thomas, J. E.: Digestion and the Nervous System: A Review of the Literature, Am. J. Digest. Dis. **10**:201, 1943.

2. Wolf, S., and Wolff, H. G.: Human Gastric Function, New York, Oxford University Press, 1943. Richards, C. H.; Wolf, S., and Wolff, H. G.: The Measurement and Recording of Gastroduodenal Blood Flow in Man by Means of a Thermal Gradientometer, J. Clin. Investigation **21**:551, 1942. Wolf, S., and Wolff, H. G.: The Gastric Mucosa, "Gastritis" and Ulcer, Am. J. Digest. Dis. **10**:23, 1943.

results and a summary of their work appear in a recent publication, which warrants careful study by any one interested in the fundamentals of gastric physiology and disease. In this volume is to be found a most excellent description of the changes occurring in the gastric mucosa involving motor activity and secretion and blood flow under varying conditions. The effect of various emotional states on gastric emptying time, the vascularity of the stomach and sensation in the stomach and the mechanisms underlying gastric symptoms are discussed in detail and bring up to date in an easily visualized manner the original observations of Beaumont on Alexis St. Martin. The measurements of blood flow in the stomach, for example, are of extreme interest. Contractions of the wall of the stomach and duodenum were accompanied by transitory acceleration of blood flow. Histamine induced a prolonged acceleration of blood flow in the gastric mucosa. The mere discussion of appetizing food was accompanied by an accelerated blood flow, and emotional states resulting in anxiety, resentment and tension had a similar effect. The general discussion by Thomas and the very careful investigations of Wolf and Wolff, which are presented in book form, together give an excellent background for any consideration of gastrointestinal physiology, particularly in relation to gastritis and gastric ulcer.

In any discussion of the "normal" responses in a given system, it is important to stress the wide variations that may be encountered. Van Liere and Northup [3] have studied the emptying time of the normal human stomach in the young adult in order to establish a criterion of the normal gastric emptying time. Sixty-nine subjects were observed under standard conditions and by repeated tests. Fluoroscopic studies showed that the average emptying of a standard meal of cereal and barium sulfate occurred at two and one-tenth hours; extremes ranged from one and five-tenths to three and three-tenths hours. These figures, of course, apply only to a given technic with a given motor meal, but they at least offer a basis for comparative studies on gastric motor activity in human beings and supplement the studies made by these authors on other age groups.

The effect of hydrochloric acid on the pyloric sphincter was studied by Quigley and his associates.[4] Their studies were carried out on dogs by the use of experimental balloons, and evidence was obtained that hydrochloric acid in the stomach exerts little or no physiologic action on the motor activities and pressure changes in the pyloric sphincter region or on the process of gastric evacuation. In the duodenum, hydrochloric acid is moderately effective in suppressing the pyloric antrum and thus retards gastric evacuation, presumably to bring about a more complete neutralization of acid values in the duodenum.

Winfield and Kaulbersz [5] found that solutions of dried bile or bile salts induced gastric hunger contractions when placed in a fasting dog's stomach, an action which was inhibited by subcutaneously injected atropine sulfate. If introduced during the contraction phase, bile, choline, potassium chloride, magnesium salts and calcium chloride cause inhibition of gastric contractions in many instances. Potassium chloride when introduced in the fasting state has an action similar to that of bile. Apparently smooth muscle activity is similar to that of the skeletal muscle with

3. Van Liere, E. J., and Northup, D. W.: The Emptying Time of the Normal Human Stomach in the Young Adult, Gastroenterology **1**:279, 1943.

4. Quigley, J. P.; Read, M. R.; Radzow, K. H.; Meschan, I., and Werle, J. M.: The Effect of Hydrochloric Acid on the Pyloric Sphincter, and Adjacent Portions of the Digestive Tract, and on the Process of Gastric Evacuation, Am. J. Physiol. **137**:153, 1942.

5. Winfield, J. M., and Kaulbersz, J.: Influence of Bile on Gastric Motility, J. Pharmacol. & Exper. Therap. **76**:97, 1942.

respect to liberation of potassium. Cicardo [6] has observed that electric stimulation of stomach strips or application of acetylcholine in concentrations that produce rhythmic contractions caused a liberation of potassium. This effect was increased by physostigmine. Atropine prevented the liberation of potassium by acetylcholine. Slaughter, Goddard, and Henderson [7] present evidence that the effects of morphine on the stomach can be potentiated by a cholinergic drug. Prostigmine methylsulfate was used as the potentiating drug. When inactive doses of morphine were given after subliminal doses of prostigmine methylsulfate, a typical morphine-like effect was seen in the stomach, as shown by a rise in tonus and rhythmic activity above the normal level. Individual inactive doses of morphine and prostigmine methylsulfate combined in one injection produced a typical morphine-like effect. The effects of atropine, prostigmine, epinephrine and calcium on the movements of the fasting human stomach were studied by Anderson and Morris,[8] using a modification of Carlson's balloon method. The drugs were administered subcutaneously, intramuscularly and intravenously during different phases of gastric activity. In small doses atropine caused an increase in the frequency and amplitude of hunger contractions and a slowing of the pulse, but a second small dose apparently had a sensitizing effect, and thereby an antiparasympathetic action was obtained. In large doses the drug inhibited the movements of the stomach and quickened the heart beat. Prostigmine was shown to have an excitor effect on gastric motility, which was not prevented by premedication with atropine unless the latter was given in large doses. Epinephrine in small doses occasionally increased gastric motility, but in large doses it consistently had a sedative action, as did calcium. The inhibitory action of calcium on the fasting contractions of the stomach was accompanied by a slowing of the heart rate, indicating vagal activity.

Further studies on the relation between low oxygen tension and gastric emptying time are to be found in an article by Stickney and Van Liere.[9] In this investigation the gastric emptying time after a standard meal was determined for 5 dogs during discontinuous exposure to reduced oxygen tension simulating altitudes of 12,000, 16,000 and 18,000 feet. The usual delay in gastric emptying produced by anoxia was found to be gradually reduced in every case. The return to normal gastric emptying under these conditions was complete at tensions of 100 mm. of oxygen and 86 mm. of oxygen. At 80 mm. of oxygen tension (18,000 feet, equivalent), only 1 dog out of 5 showed a complete return to normal levels. Considerable individual variation was found in the time for complete return to normal gastric emptying. The persistence of this adaptation of anoxia to the periods of discontinuous exposure was from less than a week to over six months. Since gastric emptying time as an index of function may reveal adequacy of the adjustment of the compensatory mechanism during anoxia, the authors suggest that it may be regarded as another criterion of acclimatization. In an attempt to find a simple substance which would reduce to normal the increased gastric emptying time produced by anoxia, Stickney [10] investigated the effect of oil of peppermint, dehydrocholic acid and disodium

6. Cicardo, V. H.: Liberation of Potassium During Contractions of Stomach, Rev. Soc. argent. de biol. **17**:81, 1941.

7. Slaughter, D.; Goddard, A. B., and Henderson, W. M.: Some New Aspects of Morphine Action: Effect on the Stomach, J. Pharmacol. & Exper. Therap. **76**:301, 1942.

8. Anderson, W. F., and Morris, N.: The Effects of Atropine, Prostigmine, Adrenaline and Calcium on the Movements of the Fasting Human Stomach, J. Pharmacol. & Exper. Therap. **77**:258, 1943.

9. Stickney, J. C., and Van Liere, E. J.: Acclimatization of Low Oxygen Tension in Relation to Gastric Emptying, Am. J. Physiol. **137**:160, 1942.

10. Stickney, J. C.: Effect of Oil of Peppermint, Dehydrochloric Acid and Disodium Phosphate on Gastric Emptying Time in Dogs, Proc. Soc. Exper. Biol. & Med. **52**:274, 1943.

phosphate. These agents were chosen because they have been reported to decrease gastric emptying time in human beings and because they have little or no complicating side effects. No significant changes were noted after the administration of any of these preparations.

In order to evaluate more properly the factor of anoxia in acute gastric dilatation, a comparative study was made by Johnson and Mann [11] on the effects of anesthetics on gastric tonus and motility in the trained dog. Studies were made on animals in which the extrinsic gastric nerves were present and on animals that had undergone vagotomy and splanchnicectomy. It was found that anesthetics had either a depressing effect on gastric tonus and motility or no effect at all. The degree of motor activity was in general directly proportional to the degree of anesthesia produced, regardless of the agent used. The authors conclude that this effect is not mediated through the vagus or splanchnic nerves but is due to a primary action on the peripheral gastric motor mechanism. The relative quantity of oxygen in the blood and tissues did not appear to be a determining factor. Striking individual susceptibility was noted, as might have been expected. Premedication with morphine and atropine definitely prolonged the depressing effect of ether, an important point in relation to preoperative medication. The depth of the anoxia appeared to be more important than its duration.

Necheles and his collaborators [12] made determinations of gastric motility in dogs following the injection of various pyrogens. Pentnucleotide, thymus and yeast nucleic acid, Bacillus coli vaccine, triple typhoid vaccine and a crystalline preparation of a bacterial pyrogen were used. In a great number of experiments depression of the gastric motility resulted, with no change in rectal temperature and with no subjective signs in most of the animals. This depression of motor activity was prolonged. The relation of this finding to "dyspepsia" during infections of the upper respiratory tract and other infectious diseases in which no or only a slight elevation of body temperature occurs is discussed. The authors feel that the threshold of the temperature center is higher than that concerned with gastric motility. They also suggest that preparations of depressants of gastric motility and secretion, such as pepsin and enterogastrone, may be contaminated with small amounts of pyrogenic substances.

The close relationship between changes in gastric and duodenal tonus and the resistance of the sphincter of Oddi were studied by Leskovar.[13] Manometric readings of alterations in the secretory pressure in the bile duct were recorded in rabbits and dogs at the same time that intragastric pressures were recorded. Heat applied to the skin produced an increase in gastric pressure and a similar increase in the resistance of the sphincter of Oddi. Emesis in dogs caused an especially marked decrease of sphincter tonus, and the subcutaneous injection of atropine also decreased the tonus of the duct sphincter, but pilocarpine increased it. A parallel relationship was seen to exist between changes in gastric and duodenal pressure and changes in tonus of the sphincter of Oddi. Apparently the determining factor influencing the functional activity of the distal portion of the bile duct was the internal pressure in the stomach and duodenum.

11. Johnson, C. R., and Mann, F. C.: The Effect of Anesthetics on Gastric Tonus and Motility with Special Reference to Acute Gastric Dilatation, Surgery **12**:599, 1942.

12. Necheles, H.; Dommers, P.; Weiner, M.; Olson, W. H., and Rychel, W.: Determination of Gastric Motility Without Elevation of Body Temperature Following Injections of Pyrogens, Am. J. Physiol. **137**:22, 1942. Necheles, H.: Depression of the Stomach by Nonspecific Substances, Proc. Inst. Med. Chicago **14**:345, 1943.

13. Leskovar, R.: Function of the Sphincter of Oddi, Arch. f. exper. Path. u. Pharmakol. **197**:361, 1941.

Some confirmation of Alvarez' conception of an intestinal gradient is to be found in an article by Chang and Hsu [14] on the chemical excitability of the isolated small intestine of the rabbit. Under standard conditions, segments were taken from different levels of the intestinal tract and were simultaneously studied as to their relative excitability. Segments from the upper levels of the intestine were generally more sensitive to acetylcholine, while those from the lower levels were more sensitive to epinephrine. This gradient of chemical excitability was easily upset by shock and asphyxia of the animal. The stimulating action of barium, physostigmine, histamine, pilocarpine and choline and the depressing action of atropine, potassium and magnesium appeared to be about equal in all the segments. The difference in excitability of the intestinal musculature to the neurohormone was regarded as an innate property of the muscle fibers at the different levels.

The effect of intravenously administered dextrose on the motor activity of the stomach and intestine was studied by Belenkov [15] and is of interest in relation to its possible effects following routine intravenous therapy. In fasting dogs, a 20 cc. dose of a 10 per cent solution of dextrose lowered the motor activity of the intestine and reduced the amplitude of and increased the intervals between the contractions, and a similar dose of a 20 per cent solution further inhibited intestinal contractions and increased the interval of contractions to twenty minutes. This dose also affected gastric activity, shortening the periods of hunger contractions and lengthening the intervals. While gastric hunger contractions continued, intestinal activity was not affected by dextrose. Twenty cubic centimeters of a 30 per cent solution of dextrose had an even greater effect on gastric and intestinal activity. In the intervals between intestinal contractions there were periods of complete rest. These responses were observed in an animal with an intact sympathetic nervous system. For an animal with a denervated intestinal tract, a dose of 40 cc. of a 40 per cent solution of dextrose was required before a distinct depression of the intestinal contractions could be noted. The application of such observations to the routine care of patients postoperatively would seem to indicate that the depressing effect of anesthesia and preoperative medication would be augmented and prolonged by the use of very hypertonic solutions of dextrose and that, as a rule, such solutions should be avoided.

In vitro confirmation of the effect of concentrated solutions of dextrose is to be found in the studies of Feldberg and Solandt.[16] These authors studied the effect of sugar and allied substances on the isolated small intestine and demonstrated the stimulating effect of optimal amounts of dextrose or certain other sugars on smooth muscle contraction of intestinal segments. In the absence of dextrose, tonic and rhythmic activity gradually ceased, even after stimulation by acetylcholine and other cholinergic drugs. The addition of small amounts of dextrose to the immersion fluid had a stimulating effect on the longitudinal intestinal muscle, but large doses of dextrose, galactose and mannose produced immediate inhibition. In this study differences in the excitability of circular and longitudinal muscle are discussed in relation to general properties of smooth muscle contraction. That the tonicity of solutions affects the motor activity of the intestine is further shown in the studies of Lignon,[17] who studied variations in intraluminal jejunal pressure in dogs follow-

14. Chang, P. Y., and Hsu, F. Y.: The Chemical Excitability of the Isolated Rabbit Small Intestine, Quart. J. Exper. Physiol. **31**:299, 1942.

15. Belenkov, N. Yu.: Effect of Glucose on the Motor Activity of the Stomach and Intestines, J. Physiol. USSR **30**:704, 1941.

16. Feldberg, W., and Solandt, O. M.: Effects of Sugar and Allied Substances on the Isolated Small Intestine of the Rabbit, J. Physiol. **101**:137, 1942.

17. Lignon, E. W., Jr.: Cathartic Salts on Motility of Thiry-Vella Jejunal Loops, Proc. Soc. Exper. Biol. & Med. **52**:282, 1943.

ing the use of isotonic and hypertonic solutions of sodium chloride, sodium sulfate and magnesium sulfate. Even with these cathartic salts, very hypertonic solutions (5 times isotonicity) caused a temporary depression of motility with short periods of spasticity and nausea. The rate of contraction was unaffected by the agents employed. Hazelton and Fortunato [18] made an evaluation of the cathartic action of bile salts. The threshold cathartic dose of bile salts compound for mice was determined, and one-half this dose was administered to these animals daily for a long period. At various intervals the threshold cathartic dose was given to the treated animals and to a similar number of controls. The results indicate that bile salts produce active catharsis in mice, that there is no tolerance or accumulation and that an appreciable degree of increased susceptibility to the cathartic action of bile salts is produced by their daily administration. This increased susceptibility is specific, as evidenced by the fact that the daily administration of bile salts did not influence the threshold cathartic dose of senna. A somewhat similar method was employed by Loewe and his associates [19] in attempting to evaluate the influence of thiamine on laxative action. The threshold cathartic dose of phenolphthalein was determined in experiments on monkeys, and subsequently thiamine was administered over a varying period in conjunction with this dose. The experiments gave no support to the assumption of a synergistic influence of vitamin B_1 on laxative action.

Differentiation between nonpropulsive and propulsive motility in the ileum and colon forms the basis of further studies by Adler, Atkinson and Ivy.[20] On human subjects with an ileostomy or colostomy observations were made of both types of motor activity. Intramuscular administration of morphine in ordinary clinical doses increased the tone and amplitude of the nonpropulsive type of rhythmic contractions of the segments of the distal portion of the ileum. The propulsive activity of the ileum was uniformly decreased. Dilaudid had a similar effect. Morphine sulfate, in the same doses, usually increased the tone and amplitude of the nonpropulsive type of rhythmic contractions of the segments in the descending colon. In 9 instances in which the colon was manifesting diarrhea the administration of morphine abolished the colostomy discharge by decreasing propulsive motor activity and by reducing tone and segmentation. Atropine produced a decrease in the total motility in the descending colon, with a uniform diminution of propulsive motility. The use of this drug partially antagonized the effect of morphine, providing evidence that the combined use of these drugs in the treatment of severe gastrointestinal pain is logical. Morphine sulfate delays the ileal and colonic passage of material in man primarily by interfering with or diminishing propulsive motility. The authors suggest that morphine causes dyskinesia of the small and large intestine and that motor activity of adjacent segments of the bowel must be coordinated in order that effective propulsion may occur. Further detailed studies on such coordination are to be found in a subsequent paper by Atkinson, Adler and Ivy.[21] Studies were made on human subjects by continuous records during seventy periods of at least one hundred and fifty minutes each. The simultaneous injection of a solution of posterior pituitary, prostigmine methylsulfate and ergotamine tartrate was found to cause a

18. Hazelton, L. W., and Fortunato, F.: An Evaluation of the Cathartic Action of Bile Salts Following Acute and Chronic Administration to Mice, J. Am. Pharm. A. (Scient. Ed.) **31**:60, 1942.

19. Loewe, S.; Loewe, I., and Knox, R., Jr.: Thiamine Influence upon Laxative Action, Am. J. Digest. Dis. **10**:65, 1943.

20. Adler, H. F.; Atkinson, A. J., and Ivy, A. C.: Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man, Arch. Int. Med. **69**:974 (June) 1942.

21. Atkinson, A. J.; Adler, H. F., and Ivy, A. C.: Motility of the Human Colon: The Normal Pattern, Dyskinesia and the Effect of Drugs, J. A. M. A. **121**:646 (Feb. 27) 1943.

prompt and prolonged increase in the propulsive motility of the human colon without side reactions. It was shown that morphine sulfate is not an antispasmodic in the sense that all motility is inhibited. As previously indicated, it increases the tone and nonpropulsive motility and definitely decreases or abolishes propulsion. Of the various "antispasmodics" studied, atropine and trasentin (a proprietary synthetic ester of diphenylacetic acid and diethylaminoethanol) proved to be the most potent depressants. Intramuscular injections of atropine sulfate may abolish all spontaneous motility of the colon for a brief period, whereas trasentin is less likely to do so. The latter may depress nonintegrated motility in such a manner that propulsion is favored and a normal gradient established. In dogs, the effect of these drugs is more striking on the distal than on the proximal portion of the colon. The authors rightly point out that the ideal "spasmolytic" drug for the colon has yet to be discovered.

Hallenbeck and his associates [22] have studied the effect of thymoxyethyldiethylamine (929 F) on gastric and intestinal motility. The intravenous injection of this preparation in dogs caused partial or complete inhibition of spontaneous and postprandial gastric motility in some instances. It usually caused transient inhibition of postprandial and spontaneous motility of duodenal and upper jejunal loops, but appeared to have no effect on the terminal portion of the ileum. Burchell and Varco [23] conclude that this drug and another of the phenoxyethers (N'-ethyl-N'-diethyl-aminoethylaniline) have a nonspecific protective action against smooth muscle contraction. They seem to have a strong preferential inhibition on the histamine type of smooth muscle reaction. With large doses of thymoxyethyldiethylamine administered subcutaneously, some evidence of lowered sensitivity to pain was observed. Complete analgesia was not noted, although this had been claimed by some previous investigators.

According to Canonico and Mann,[24] obstruction of the common bile duct by ligation was followed in animals by a marked decrease of activity in exteriorized loops of jejunum and ileum during the first two weeks after operation. Subsequently intestinal activity increased but never returned to normal in the jaundiced animals. The decrease of motor activity occurred in both fasting and digesting states but was more noticeable in the latter. It is suggested that the retention of biliary constituents in the blood, particularly bile salts, may be the cause of alteration in intestinal activity.

Svien and Mann [25] have studied motor activity of the jejunum and the upper part of the ileum following distention of the gallbladder and the urinary tract. Distention of the gallbladder apparently produced no change in the peristaltic pattern of the jejunum or ileum. Sudden distention of the urinary bladder produced diminution of duodenal activity and inhibited activity in all segments of the small intestine, the greatest effect being noted in the upper segments. Distention of the upper part of the urinary tract produced inhibition of motility in the jejunum and ileum, which persisted as long as distention was maintained and in some cases for variable periods up to five minutes after the distending pressure had been released. The authors believe that their results are consistent with the hypothesis of a gradient of irritability

22. Hallenbeck, G. A.; Code, C. F., and Mann, F. C.: The Effect of Thymoxyethyldiethylamine (929 F) on Gastric and Intestinal Motility: An Experimental Study, Gastroenterology **1**:588, 1943.

23. Burchell, H. B., and Varco, R. L.: The Anti-Histamine Activity of Thymoxyethyldiethylamine and n'Ethyl-n'Diethylaminoethylaniline as Judged by the Gastric Response to Histamine, J. Pharmacol. & Exper. Therap. **75**:1, 1942.

24. Canonico, A., and Mann, F. C.: Intestinal Activity After Obstruction of Common Bile Duct, Surgery **13**:81, 1943.

25. Svien, H. J., and Mann, F. C.: Intestinal Activity Following Distention of the Gall Bladder and Urinary Tract: An Experimental Study, Surgery **13**:67, 1943.

from the duodenum caudalward. Since the upper segments of the small intestine are more irritable than are the lower segments, it would seem that the duodenum and the upper portion of the jejunum are less readily inhibited and less readily kept under inhibition by a given stimulus than is the lower part of the ileum. These experiments are of additional clinical interest inasmuch as they tend to reproduce the picture of intestinal obstruction which is occasionally seen in relation to sudden obstruction of some portion of the urinary tract.

A further consideration of the effects of anesthesia on intestinal motility is to be found in an article by Wakim and Mann,[26] who studied the combined results of ether anesthesia and exploratory laparotomy. Such a procedure abolished intestinal activity for at least four hours, but in twenty-four hours the activity of the intestine was practically normal. Section and anastomosis of the intestine abolished intestinal activity for about forty-eight hours, after which rhythmic segmentation and peristalsis reappeared. Feeding inhibited activity in the loop when the site of section and anastomosis was proximal to the loop under observation. After the sixth postoperative day the intestines resumed normal motor activity.

The mechanism of intestinal inhibition by cyclopropane anesthesia was studied by Youmans and his associates,[27] this anesthetic producing great diminution or complete abolition of the rhythmic contractions of the dog's intestine, even when the adrenal glands had been denervated and demedullated. The inhibition was still present under hyperventilation with the cyclopropane-oxygen mixture. The authors conclude that the inhibition of intestinal motor activity by cyclopropane is not dependent on the liberation of epinephrine from the adrenal medulla or on a low oxygen tension in the alveolar air. The relationship between such motor inhibition and postoperative distention is obvious, and the observations of Puestow [28] on a human subject are of interest. In his subject Puestow was able to observe several loops of the jejunum and the upper part of the ileum, as well as the ascending colon, through a large hernial sac. A definite relationship was noted between the motility of the small intestine and that of the ascending colon, the latter being inactive when the small bowel was contracting vigorously, and vice versa. The author was able to confirm the observation that opiates, physostigmine, prostigmine methylsulfate and the choline derivatives, which stimulate motility of the small bowel, inhibit the colon, and that, conversely, solutions of posterior pituitary and pitressin produce powerful contractions of the colon but diminish motor activity of the small bowel. Confirmatory observations were made on 13 other patients with portions of the bowel exposed to direct vision. One important conclusion should be stressed, in the opinion of the reviewer—namely, that postoperative distention may be due in large part to the paralyzing action of morphine on the colon. It is entirely possible that the action of this drug, which is so universally used preoperatively and postoperatively, may be one of the most important factors in the distention and abdominal discomfort subsequent to a major abdominal operation and that its use might be appreciably curtailed with advantage to the patient.

The close relationship between the cerebral cortex and the motor action of the digestive tract is emphasized by the studies of Booligin,[29] who investigated the move-

26. Wakim, K. G., and Mann, F. C.: Effects of Some Intra-Abdominal Operative Procedures on Intestinal Activity: An Experimental Study, Gastroenterology **1**:513, 1943.

27. Youmans, W. B.; Enos, R. W.; Karstens, A. I., and Aumann, K. W.: The Mechanism of Intestinal Inhibition by Cyclopropane Anesthesia, Anesthesiology **3**:303, 1942.

28. Puestow, C. B.: Intestinal Motility and Postoperative Distention: Experimental and Clinical Studies, J. A. M. A. **120**:903 (Nov. 21) 1942.

29. Booligin, I. A.: The Relation Between the Cerebral Cortex and the Motor Action of the Digestive Tract, Arch. di sc. biol. **54**:65, 1939.

ments of the fundic and pyloric regions of the stomach, of the duodenum, of various portions of the alimentary tract and of the parotid glands. The influence of the cerebral cortex on gastrointestinal motility is accomplished by short cortical impulses caused by sudden "conditioned stimuli" and prolonged cortical impulses caused by prolonged exposure to "food surroundings." The effect of the short impulses appears to depend on the character of the conditioned reflex; that of the more prolonged stimulus, positive or negative, on the section of the alimentary tract involved and on its functional state. "Short" conditioned stimuli caused cortical stimuli initiating gastric and intestinal motility within a few seconds or rarely after one to three minutes and producing an effect lasting from thirty seconds to five minutes. The author believes that by such means the cortex not only regulates motility of the stomach but adapts it rapidly to changing environmental conditions.

Sheehan [30] has elaborated earlier studies on the relationship of the hypothalamus to the large bowel. He obtained results confirmatory of those of others, indicating that adequate hypothalamic stimulation, particularly in the lateral hypothalamic area, is followed by inhibition of peristalsis in the large bowel as well as in the intestine and stomach and that such effects are more marked in the colon than elsewhere. There are adequate grounds, he believes, for accepting the concept of a sympathetic center regulating gastrointestinal activity and located in this area.

Studies on certain aspects of the motor innervation of the colon have received continued attention by Ivy and his collaborators.[31] One series of experiments has been undertaken to supply evidence on certain pertinent questions concerning the chemical mediators of nerve impulses from various nerves to the colon, the region of the colon which responds to stimulation of a given nerve, the pathway by which pelvic nerve impulses influence upper levels of the colon and the similarity between colonic and vesical motor activity following stimulation of the pelvic nerves. In experiments which were carried out on dogs, pigs and monkeys, the authors come to the conclusion that the pelvic nerves to the musculature of the colon are cholinergic. Electrical stimulation of the pelvic nerves causes longitudinal and circular contraction of the descending and the distal portion of the colon. These nerves influence upper levels of the colon via nerve pathways located in the wall of the colon. A dual contractile and tonus mechanism in response to stimulation of the pelvic nerves does not exist in the colon, as has been claimed to exist in the urinary bladder. Electrical stimulation of the vagus nerve is ineffective in producing colonic motility in the dog. Only inconstant cecal contractions were noted in the pig and in the monkey. The hypogastric nerves to the musculature of the colon are adrenergic, and electrical stimulation usually causes a circular contraction which is confined to the distal portion of the colon. The fibers of the celiac root of the inferior mesenteric ganglion which act on the colon are adrenergic, and electrical stimulation of them usually causes a circular contraction which is confined to the descending colon.

Studies on the concentration of acetylcholine in the alimentary tract were made by Bacq and Goffart.[32] The highest concentrations in dogs were found in the upper part of the jejunum, and the lowest concentrations, in the esophagus and in the colon.

30. Sheehan, D.: Relationship of the Hypothalamus to the Large Bowel, Am. J. Digest. Dis. **9**:361, 1942.

31. Wells, J. A.; Mercer, T. H.; Gray, J. S., and Ivy, A. C.: The Motor Innervation of the Colon, Am. J. Physiol. **138**:83, 1942.

32. Bacq, Z. M., and Goffart, M.: Free and Combined Acetylcholine in Intestinal Tract, Schweiz. med. Wchnschr. **71**:310, 1941.

The mucosa always contains less acetylcholine than the muscularis. There appeared to be no parallelism between the tissue concentration of vitamin B_1 and that of acetylcholine.

The conclusion by several investigators that stimulation of the hypothalamic region simultaneously regulates both sympathetic and parasympathetic divisions of the autonomic nervous system finds support in the studies of Mautner and Yetwin [33] and in those of Oppenheimer and his associates.[34] The former noted in rats that injections of metrazol resulted in a cessation of gastric motility with an associated moderate increase in secretory activity. They felt that the effect on gastric motility could not be attributed to an increased output of epinephrine but was probably due to a central effect. Bulbocapnine has been shown to stimulate both the sympathetic and the parasympathetic centers. Oppenheimer and his associates studied the effect of such stimulation in dogs by subcutaneous injection of bulbocapnine phosphate. Sympathetic effects, as regards intestinal motility, were the most important, and the amplitude of contraction was diminished. In vagotomized dogs, loops of intestine just below the duodenum showed an increased amplitude of contraction after medication, but in the region of the ileocecal valve inhibition was noted. In splanchnicectomized dogs, the vagus mechanism was activated in respect to the amplitude of intestinal contractions, except for the effect on the blood sugar levels, which were raised. The drug did not change the rate of intestinal contractions. The effect of vagotomy and of sympathectomy on the sensitivity of intestinal smooth muscle to epinephrine was studied by Youmans, Karstens and Aumann.[35] The only denervation which produced extreme hypersensitivity of the intestinal smooth muscle to epinephrine was that which involved sectioning of axons passing to the intestine from cell bodies located in the preaortic ganglions.

The probability that both cholinergic and adrenergic effects may be noted simultaneously, possibly owing to central stimulation in the vicinity of the hypothalamic areas, receives further confirmation from the observations by Milhorat and his collaborators.[36] These authors carried out experiments in which they subjected the intestines of rabbits to venous blood of patients showing anxiety or fear. Unlike the effects of blood from normal controls, the specimens of blood taken during states of marked emotional disturbance caused definite changes in the motor activity of the intestinal muscle under study. These effects were not like the relatively simple response observed with epinephrine or acetylcholine in similar experiments, but were mixed in nature, generally tending to resemble those of cholinergic drugs. An interesting finding was that blood taken from psychotic patients in quiescent periods showed none of the effects on motor activity produced by blood taken from patients in an anxiety state. The mechanism underlying the motor, secretory and vascular changes visualized by Wolf and Wolff, which have already been referred to, may thus receive some experimental confirmation.

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33. Mautner, H., and Yetwin, I. J.: Effects of Pentamethylenetetrazol (Metrazol) on the Stomach, J. Am. Pharm. A. (Scient. Ed.) **32**:17, 1943.

34. Oppenheimer, M. J.; Glyer, N. M., and Hamilton, R. H.: Intestinal Motility as Influenced Through Extrinsic Nerves as a Result of Central Stimulation by Bulbocapnine, Proc. Soc. Exper. Biol. & Med. **51**:79, 1942.

35. Youmans, W. B.; Karstens, A. I., and Aumann, K. W.: Effect of Vagotomy and of Sympathectomy on the Sensitivity of Intestinal Smooth Muscle to Adrenalin, Am. J. Physiol. **137**:87, 1942.

36. Milhorat, A. T.; Small, S. M.; Doty, E. J., and Bartels, W. E.: Probable Mechanism by Which Somatic Changes in Certain Emotional States Are Mediated, Proc. Soc. Exper. Biol. & Med. **53**:23, 1943.

Emilsson [37] found that the l-isomers of adrianol, corbasil and synephrine always inhibited the rabbit intestine, while the d-isomers inhibited in large doses and stimulated in small doses. Other variations in the optical isomers of these drugs are discussed. The mechanism involved in the inhibition of intestinal motor activity is in part elucidated by the influence of sympathicolytic agents, such as bee venom and ergotamine, on the action of epinephrine substitutes. The same author [38] noted that the action of epinephrine and similar drugs in inhibiting intestinal activity is momentary and is completely abolished by a sufficient dose of bee venom or ergotamine, whereas drugs like amphetamine, whose inhibiting action develops slowly, are not abolished by such sympathicolytic agents. Amphetamine and similar drugs must produce their effect by direct muscular depression and not through action on the sympathetic nerve endings or specific receptors, as does the first group.

Youmans and his associates [39] studied the relation of the extrinsic nerves of the intestine to the inhibitory action of atropine and scopolamine. Atropine appears to exercise an inhibitory action on the tonus and rhythmic activity of the intestine independently of the extrinsic nerves. Its action is not reduced by vagotomy, and although sympathectomy results in an increased sensitivity of the intestine to the inhibitory action of the drug, it seems that the action of atropine is probably accomplished by a local action of the drug on the neural or muscular elements of the intestinal wall, in that it renders smooth muscle unresponsive to acetylcholine, which is being produced at a basal level in the intestine independently of the extrinsic nerves. The actions of scopolamine were indistinguishable from those of atropine. Studies on isolated intestinal loops by Shaw [40] indicate that the site of the depressant action of barbiturates on the intestine is in the postganglionic fibers and the muscle cells. This depressant action is abolished by physostigmine, there being a reciprocal antagonism between these two drugs.

Gernandt [41] has investigated the biologic activity of the P substance obtained by alcoholic extraction of rabbit or horse intestinal wall. This substance causes a transitory fall in blood pressure and considerable rise in intestinal motility. In vivo preparations of the P substance applied either locally or intravenously in rabbits produce movements of the small intestine but not of the colon and increase intestinal peristalsis. Another substance, indole, has been found by Garcia-Blanco and his associates [42] to have an inhibitory action on the rhythmic movements of the isolated rabbit intestine. With a 1 per cent concentration of indole such movements were suppressed, and when the substance was injected into the lumen of the intestine in a concentration of 0.017 per cent, movements ceased. Substitution of a hydrogen ion by a methyl, acetic or propionic radical made the substance inactive.

37. Emilsson, B.: The Action of the Optical Isomers of Adrianol, Corbasil, Synephrine and Ephedrine on Isolated Intestine, Acta physiol. Scandinav. **3**:275, 1942.

38. Emilsson, B.: Influence of Sympathicolytic Agents on the Action of Adrenaline Substitutes on Isolated Intestine: I. Bee Venom and Ergotamine, Acta physiol. Scandinav. **3**:335, 1942.

39. Youmans, W. B.; Karstens, A. I., and Aumann, K. W.: Relation of the Extrinsic Nerves of the Intestine to the Inhibitory Action of Atropine and Scopolamine on Intestinal Motility, J. Pharmacol. & Exper. Therap. **77**:266, 1943.

40. Shaw, F. H.: The Action of Barbiturates on the Isolated Intestine, Australian J. Exper. Biol. & M. Sc. **20**:117, 1942.

41. Gernandt, B.: The Biological Activity of the P Substance, Acta physiol. Scandinav. **3**:270, 1942.

42. Garcia-Blanco, J.; del Castillo, J., and Rodeles, F. J.: Effect of Indol on Intestinal Motility, Rev. Soc. argent. de biol. **17**:473, 1941.

The mode of action of phenolphthalein has been studied by Blick, Barardi and Wozasek.[43] Intravenous injection of this drug in dogs did not increase peristaltic activity of the small intestine. Activity of the large bowel was increased, but there appeared to be no concomitant vagal action on the heart, a finding which would support the view that the action of phenolphthalein is not due to general parasympathetic stimulation. Comparison with other drugs which are known to stimulate intestinal activity is of interest. Phenolphthalein simulates the action of barium on the intestine; the latter, however, is much stronger in action on the muscle than is phenolphthalein and affects the heart muscle, whereas phenolphthalein does not. Solution of posterior pituitary, when applied locally, acts on the intestinal musculature even more markedly than phenolphthalein. Atropine, which inhibits the motor nerves of the intestine, does not stop the cathartic action of phenolphthalein. Physostigmine, which increases motor activity apparently by vagal stimulation, also has an effect on the heart rate. It would appear, therefore, that phenolphthalein acts directly on the muscle rather than on the autonomic nerve fibers.

An excellent summary of the important recent literature concerning intestinal motility is to be found in a review by Ingelfinger,[44] who discusses some seventy-three articles in adequate detail.

Secretory Aspects.—The mechanism of gastric secretion has received considerable attention. The physiology of the parietal cells, with special reference to the formation of acid, is the subject of a discussion by Gray,[45] who presents the existing evidence bearing on the production of gastric acid. According to him, this evidence indicates that the parietal cells of the stomach secrete an isotonic solution containing chlorine, hydrogen and potassium ions. The process of formation of acid is independent of external sources of carbon dioxide. Approximately 1.5 large calories of energy are required for the production of 1 liter of parietal secretion. The energy for secretion is probably supplied by the oxidation of dextrose. All the evidence discussed satisfies the requirements of the carbonic anhydrase theory of acid formation—namely, that the carbon dioxide formed within the parietal cell by its metabolic activity is converted immediately into carbonic acid by the activity of the enzyme carbonic anhydrase. The acid then ionizes, and the resulting hydrogen ions are diverted into the parietal secretion. At the same time the bicarbonate ions are sent into the blood in exchange for an equivalent amount of chloride ions, which are then also diverted into the secretion to complete the hydrochloric acid. Such a conception receives confirmation from Davenport,[46] who states that the conclusion that the parietal cells actually secrete isotonic hydrochloric acid should be accepted until overwhelming experimental evidence to the contrary is obtained. A detailed discussion of the present knowledge of this intricate subject is to be found in a second paper by the same author,[47] and a further consideration of the same problem, in which some additional points are mentioned, is included in an article by Hollander.[48] The latter recapitulates an extensive analysis of the literature and adds his own

43. Blick, P.: Barardi, J. B., and Wozasek, O.: The Mode of the Laxative Action of Phenolphthalein, Am. J. Digest. Dis. **9**:292, 1942.

44. Ingelfinger, F. J.: The Modification of Intestinal Motility by Drugs, New England J. Med. **229**:114, 1943.

45. Gray, J. S.: The Physiology of the Parietal Cell with Special Reference to the Formation of Acid, Gastroenterology **1**:390, 1943.

46. Davenport, H. W.: The Secretion of Water as a Component of Gastric Acid Secretion, Am. J. Digest. Dis. **9**:416, 1942.

47. Davenport, H. W.: The Secretion of Acid by the Gastric Mucosa, Gastroenterology **1**:383, 1943.

48. Hollander, F.: The Chemistry and Mechanics of Hydrochloric Acid Formation in the Stomach, Gastroenterology **1**:401, 1943.

observations and experiments. The essential characteristic of parietal secretion is that it is an isotonic, or slightly hypertonic, solution of hydrochloric acid, which may contain hydrobromic acid and hydriodic acid when their salts are present in the blood stream, but nothing else. The immediate source of chlorine lies in the neutral chlorides of the blood and lymph. The entire process of hydrochloric acid formation, starting with the blood chloride and ending with the ejection of acid into the gastric cavity, requires less than one minute. The hydrochloric acid is formed by hydrolysis of the neutral chlorides of the cytoplasm, the residual alkali being neutralized immediately by the intracellular buffers. Isotonicity is attained coincident with the transference of water and hydrochloric acid into the lumen of the gland. Thus the formation of the parietal secretion constitutes a "steady state" in which the concentrations of water and hydrochloric acid as they pass out of the cells are in a fixed ratio. Apparently the parietal cells are indefatigable as long as an adequate supply of water and chlorides is maintained. The process involves chemical, osmotic, electrical and mechanical work, but as yet there is no explanation for the mechanism by which the energy for such work is provided.

Epshtein [49] studied the changes and the chemical composition of the gastric juice caused by the administration of bromides. The administration of sodium bromide produced an increase in gastric secretion, an increase in the total and free acidity and an increase in the total content of the halogens, with a certain rise in the amount of liberated potassium, the concentration of which is greater in the more acid juices. If the gastric secretion is considered as a phenomenon of membrane equilibrium of the type of "steady state," it follows that the increase in the secretion is accompanied with a rise in the acidity of the gastric juice and in the content of precisely those elements which possess a greater mobility (potassium versus sodium, and bromide versus chlorine).

A somewhat new conception of gastric contents is presented by Cope, Cohn and Brenizer.[50] These authors studied the absorption of radioactive sodium and heavy water from pouches of the body and antrum of the dog's stomach. Radioactive sodium is absorbed in small but significant quantities from the body or acid-secreting areas. Two or three times as much is absorbed when the mucosa is resting as when it is in a secreting state. The gastric antrum absorbs one hundred times as much as the acid-secreting body. Variations in the osmotic pressure of the sodium solutions and in electrolyte concentrations in the blood serum would have no significant effect on the rate of absorption of the sodium. Observations on the absorption of heavy water (D_2O) indicated that there was no significant difference in the rate of absorption between the body and the antral pouches, half of the heavy water being absorbed in approximately twenty minutes. The authors conclude that the conception that the fluid in an isolated pouch of the stomach represents secretion is obsolete and that the antrum plays a preponderant role in any observed absorption from the whole stomach. On the assumption that the gastric membrane handles heavy water as it does ordinary water, the authors conclude that there is a rapid exchange of the latter between the gastric contents and the body fluids; such an exchange would provide a major reason for isotonicity.

49. Epshtein, I. A.: Distribution of Bromide in the Organism After the Administration of Br Salts, Ark. biol. Nauk **56**:59, 1939.

50. Cope, O.; Cohn, W. E., and Brenizer, A. G., Jr.: Gastric Secretion: II. Absorption of Radioactive Sodium from Pouches of the Body and Antrum of the Stomach of the Dog, J. Clin. Investigation **22**:103, 1943. Cope, O.; Blatt, H., and Ball, M. R.: Gastric Secretion: III. Absorption of Heavy Water from Pouches of the Body and Antrum of the Stomach of the Dog, ibid. **22**:111, 1943.

The great factor of safety in the blood supply of the stomach is exemplified by the experiments reported by Babkin, Armour and Webster.[51] Ligation of most of the gastric arteries affected the secretory function of the stomach little, except that some transient diminution of the volume of gastric secretion was evoked by sham feeding or by subcutaneous administration of histamine. Similar effects were noted in relation to the secretion of pepsin. The acidity and the total chloride concentration of the gastric juice remained unchanged after partial or almost total devascularization of the stomach, and such arterial ligation never led to the formation of peptic ulcer or even of mucosal erosions. Confirmation of these findings is to be seen in similar studies by Layne and Bergh,[52] who found that ligation of two or three of the large arteries supplying the stomach produced no significant alteration of acid gastric secretion in the dog and did not change the appearance of the gastric mucosa as viewed through the gastroscope. When the four large arteries of the stomach were ligated, the animals died within six to thirty-six hours, as a result of necrotizing lesions. Such observations demonstrate the existence of free and liberal anastomosis between the gastric, esophageal and phrenic arteries and indicate the safety with which ligation, within reason, may be practiced in surgical operations.

The observations of Hoelzel [53] on himself suggest a relationship between the hydration of the body and gastric acidity. With a diet high in protein and fat and low in carbohydrate and calories, the gastric secretion of hydrochloric acid was definitely reduced. With such a diet, as the weight of the individual fell, so did the gastric acidity. With increased calories taken as carbohydrate, the body weight rose, and hydration increased, as is well known, and with it the gastric acidity. Such a finding may bear on the statement by Hollander, already alluded to, that the secretion of parietal cells is maintained as long as an adequate supply of water and chlorides is present.

One of the most provocative contributions to the physiology of gastric secretion is that by Stefko, Andrus and Lord.[54] These authors report the effects of jejunal transplants into the wall of the stomach on the free and combined acidity of the gastric secretion and the p_H of the various parts of the mucosa of the stomach. The results of this procedure on gastric secretion consisted in a reversal of the normal response to histamine in most of the experimental animals. The fasting p_H showed little change but the p_H level after administration of histamine was considerably elevated after the implantation of the jejunal segment. The effect on the gastric analysis was similar, the average free and combined acidities during fasting being diminished after transplantation, and this decrease was accentuated by histamine. These changes occurred within forty-five minutes after the transplantation and persisted for at least four months. In 2 animals (dogs) the transplant was resected later and subsequent testing with histamine revealed normal reactions. It was found that transplants from the ileum and the colon were without effect as

51. Babkin, B. P.; Armour, J. C., and Webster, D. R.: Restoration of the Function Capacity of the Stomach When Deprived of Its Main Arterial Blood Supply, Canad. M. A. J. **48**:1, 1943.

52. Layne, J. A., and Bergh, G. S.: The Effect of Ligation of Arteries of the Stomach upon Acid Gastric Secretion and upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, Surgery **13**:136, 1943.

53. Hoelzel, F.: Gastric Acidity, Nutritional Hydration and Appetite, Am. J. Digest. Dis. **10**:121, 1943.

54. Stefko, P.; Andrus, W. deW., and Lord, J. W., Jr.: The Effects of Jejunal Transplants on Gastric Acidity, Science **96**:208, 1942. Lord, J. W., Jr.; Andrus, W. deW., and Stefko, P.: Comparative Effects of Pedicle Grafts from Different Levels of Intestinal Tract on p_H of Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**:100, 1943.

regards any influence on the p_H of the gastric mucosa after injection of histamine. On the other hand, with both duodenal and jejunal grafts, the p_H of the mucosa rose after the administration of histamine, the jejunal grafts being somewhat more effective. Such experimental findings are of the utmost importance, and the implication is clear. It is obvious that the depression of gastric secretion was evoked by some hormonal stimulation rather than by the actual amount of neutralizing substance secreted by the transplant. Whether this effect was through some medium such as enterogastrone remains to be determined, but the findings are of extreme significance inasmuch as they suggest an entirely new and apparently physiologic approach to the treatment of peptic ulcer. Jejunal transplants in human patients with ulcer have already been performed as a result of these experiments, but sufficient time has not elapsed to warrant conclusions as to the validity of such a surgical procedure.

Further evidence of the hypothetic gastric secretory hormone, gastrin, is to be found in reports by Komarov.[55] An apparently specific secretagogue can be consistently extracted from the pyloric mucosa of the dog and of the hog by methods previously described. The pyloric extracts were so purified that they stimulated a secretion of highly acid gastric juice virtually devoid of peptic power but had no effect on pancreatic or biliary secretion, did not influence blood pressure, had no toxic effects and were free from histamine. The results were not abolished by atropine, vagotomy or splanchnicectomy.

Scott, Moe, and Brunschwig [56] have made further studies on the properties of the gastric secretory depressant found in gastric juice. In patients with achlorhydria, gastric cancer or pernicious anemia this factor is present in relatively high concentration. It is contained in the flocculent precipitate obtained by the addition of four volumes of absolute alcohol to neutralized gastric juice. Investigation has shown that the method used for extraction of the gastric secretory-depressant factor from urine (urogastrone) does not extract the gastric secretory depressant from an alcohol precipitate of human gastric juice; hence these two factors are not identical. Urogastrone has been further studied by Schiffrin and Gray [57] in enterectomized dogs, in order to obtain further evidence that it is not identical with enterogastrone. Their experiments were carried out in animals in which the entire small intestine, from the pylorus to the ileocecal sphincter, was removed, together with excision of the body of the pancreas and ligation of the common duct. Urogastrone effectively inhibited the volume of gastric secretion and the output of free acid. Similar results were obtained in dogs with vagotomized total gastric pouches. No evidence was obtained that urogastrone inhibits gastric secretion through the liberation of enterogastrone.

Attempts to determine the relationship of the neurohypophysis to gastric secretion were made by Gross and his collaborators.[58] Section of the pituitary stalk in dogs resulted in a high degree of polyuria but no alteration in the acidity of the gastric juice. The injection of pitressin tannate into dogs with normal gastric pouches produced no alteration in either volume or acidity.

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55. Komarov, S. A.: Studies on Gastrin: II. Physiological Properties of the Specific Gastric Secretogogue of the Pyloric Mucous Membrane, Rev. canad. de biol. **1**:377, 1942.

56. Scott, V. B.; Moe, R., and Brunschwig, A.: Further Studies on the Properties of the Gastric Secretory Depressant in Gastric Juice, Proc. Soc. Exper. Biol. & Med. **52**:45, 1943.

57. Schiffrin, M. J., and Gray, J. S.: The Effect of Urogastrone on Gastric Secretion in Enterectomized Dogs, Am. J. Physiol. **137**:417, 1942.

58. Gross, E. G.; Ingram, W. R., and Fugo, N. W.: Experiments on the Relationship of the Neurohypophysis to Gastric Secretion, Am. J. Digest. Dis. **9**:234, 1942.

The multiplicity of factors entering into the various phases of gastric digestion alone is indicated in the detailed studies of Ohlsen [59] on the distribution of enzymes in various parts of the gastric mucosa, as studied by histochemical methods. Diaminopeptidase and aminopolypeptidase are distributed independently of each other in the pyloric and fundic mucosa. The former is predominant in the region of the pit epithelium and the neck of the chief cells, while the latter is found predominantly in the chief cells of the fundus. Pepsin is the characteristic enzyme to be found in the fundus and follows the distribution of the chief cells. Dipeptidase, aminopolypeptidase and prolinpeptidase almost alone characterize the pyloric mucosa, and in man abundant urease occurs in the surface mucosa in the region of the pylorus.

It is now generally accepted that pepsin and rennin are distinct and different enzymes, and the impression is that they are both present in gastric juice. Dotti and Kleiner,[60] by ingenious experiments on human beings, have arrived at the conclusion that no rennin is present in the gastric juice of human adults.

Various factors influencing gastric secretion have been further studied. For example, Pincus and his associates [61] conclude that the introduction of acid into the duodenum inhibits gastric secretion only if a threshold level of duodenal p_H (approximately 2.5) is attained, and that the extent of depression of gastric secretion is dependent on the level of p_H produced. One might well ask whether such changes in the duodenal p_H coincide with the production of enterogastrone. Bantin [62] noted a temporary secretory alteration in gastric activity following ligation of the ductus choledochus that accompanied the inhibition of gastric motility already alluded to. A few days after the tying of the duct, the quantity of the gastric juice increased, together with the hydrochloric acid content and the digestive power of the gastric juice. This temporary increase was followed by depression of the quantity, quality and effectiveness of the gastric juices.

The secretion of acid by the stomach is greatly increased by the subcutaneous injection of benzylimidazoline (priscol). Thiele [63] notes that the subcutaneous injection of this preparation is followed by a more constant and satisfactory result than the ordinary test meal or the use of caffeine products, but that it is apparently somewhat inferior to histamine. Unlike histamine, however, it causes no disturbing side reactions and can be given in several successive 10 mg. doses.

In addition to its effect on motor activity, the effect on gastric secretion of the histamine antagonist thymoxyethyldiethylamine (929 F) has been observed. Bourque and Loew [64] carried out experimental studies on this preparation, as well as on a similar histamine antagonist, N-phenyl-N-ethyl, N'-diethylethylenediamine (1571 F), using as stimulants to secretion histamine, pilocarpine and food. The data from these studies on dogs with gastric pouches did not support the belief that 1571 F is a specific antagonist to histamine, and although the drug reduces gastric secretion following stimulation with histamine in dogs with gastric pouches,

59. Ohlsen, A. S.: Contribution to the Histochemistry of the Stomach, Compt. rend. d. trav. du lab. Carlsberg, serie chim. **23**:329, 1941.

60. Dotti, L. B., and Kleiner, I. S.: Absence of Rennin from Adult Human Gastric Juice, Am. J. Physiol. **138**:557, 1943.

61. Pincus, I. J.; Thomas, J. E., and Rehfuss, M. E.: A Study of Gastric Secretion as Influenced by Changes in Duodenal Acidity, Proc. Soc. Exper. Biol. & Med. **51**:367, 1942.

62. Bantin, E. V.: Retention of Gall and Its Effect on the Activity of the Stomach, J. Physiol. USSR **27**:599, 1939.

63. Thiele, W.: Priscol, a New Substance for Gastric Diagnosis, Klin. Wchnschr. **19**:620, 1940.

64. Bourque, J. E., and Loew, E. R.: Effect of Histamine Antagonists on Gastric Secretion, Am. J. Physiol. **138**:341, 1943.

the reduction in secretion was nearly identical after stimulation with pilocarpine. This drug did not modify gastric secretion in dogs with gastric pouches stimulated with food. Pretreatment with 929 F failed significantly to modify the secretion from gastric pouches in dogs given injections of pilocarpine.

Injections of "prolan" into dogs decreased the secretion of the stomach juice after a standard meal, according to Eidinova.[65] The depression was most manifest on the fourth and fifth days after administration of the drug. Parrot [66] found that in dogs epinephrine markedly activates gastric secretion. Under the influence of diverse sympatholytic agents, such as yohimbine and ergotamine, the volume of secretion is increased 30 to 150 per cent compared with control levels. Activation of this secretion is inhibited by atropine. The question whether histamine and acetylcholine are brought into play after injection of epinephrine was studied. The secretion following injection of histamine differs from that produced by epinephrine in that latency time is shorter, the juice is less rich in nitrogenous substances and the secretion is not abolished by atropine.

According to Stavraky,[67] mecholyl causes a secretion of alkaline mucus from the pyloric portion of the stomach simultaneously with the secretion of acid and pepsin from the fundic pouch. From the whole stomach, fractionated injections of mecholyl cause abundant secretion of acid, whereas single doses of mecholyl cause only a scanty secretion of gastric juice of low acidity. The concentration of pepsin in the gastric juice is high as long as the secretion is acid in reaction. The concentration of pepsin is independent of the volume of secretion or of the mode of administration of mecholyl, but is directly related to the amount of mecholyl given. Preceding administrations of mecholyl also raise the concentration of pepsin in the gastric juice evoked by stimulation of the vagi.

Because of differences of opinion concerning the secretion of gastric juice during the interdigestion period, Mears [68] made observations on a group of approximately normal persons and on a group of patients with ulcer. Gastric secretion during the night was observed by means of inlying nasal tubes. During control periods mean values indicated that the secretory rate and the volume of secretion of free and of total acid were higher for the group with ulcer than for the control group. This, of course, conforms with the usual conception of gastric secretion in patients with ulcer. Atropine diminished the volume of secretion as well as the free and total acidity in both the normal group and the patients with ulcer. It is interesting to note that the decrease in these values was more pronounced in the group with ulcer.

Inhibition of peptic activity was studied by Shoch and Fogelson.[69] These authors demonstrated that mucin, magnesium trisilicate and aluminum hydroxide inhibited the peptic activity of gastric juice by decreasing the acidity, the amount of inhibition being directly related to changes in p_H. Sodium lauryl sulfate completely inhibited peptic activity, regardless of p_H, through its protein-denaturing action. The use of this substance (as Dreft) has been somewhat too widely publicized, but the inactivation of gastric pepsin by detergents should be thoroughly

65. Eidinova, M. L.: The Influence of Hormones on the Excitability of the Digestive Glands, J. Physiol. USSR **28**:354, 1940.

66. Parrot, J.-L.: Action sécrétrice de l'adrénaline sur l'estomac. Longue dureé du temps de latence. Hypothèse sur le méchanisme de Catte action, Compt. rend. Acad. d. sc. **212**:1054, 1941.

67. Stavraky, G. W.: Some Aspects of Gastric Secretion Induced by Mecholyl, Canad. M. A. J. **48**:68, 1943.

68. Mears, F. B.: The Effect of Atropine on Gastric Secretion During the Night, Surgery **13**:214, 1943.

69. Shoch, D., and Fogelson, S. J.: Peptic Inhibition, Proc. Soc. Exper. Biol. & Med. **50**:304, 1942.

investigated in man because of the possible application of such a principle to the therapy of ulcer.

The effectiveness of replacement therapy for achlorhydria has long occasioned serious doubts. The actual amount of any acid necessary to bring the p_H of the gastric contents following a normal meal to physiologic range (p_H 1.6 to 1.8) or for peptic activation (below p_H 2.0) is of such magnitude that practical aspects preclude its administration. Koehler and Windsor [70] have carried out in vitro experiments with a normal meal, rather than an Ewald test meal, and arrive at this conclusion. For achlorhydric patients ingesting a normal meal, the amount of U.S.P. hydrochloric acid needed to bring about optimum p_H values would be approximately 35 cc. Even twenty 420 mg. capsules of glutamic acid hydrochloride with a meal would fail to produce normal activity or to activate pepsin. If such findings are correct, it is obvious that the administration of hydrochloric acid therapeutically to patients with achlorhydria must have some other effect than that of acidifying gastric contents or activating pepsin.

Anacidity has little or no effect on the absorption of ascorbic acid, as shown by Chernya.[71] The urinary excretion of vitamin C in anacid patients corresponds to that in patients with normal secretions, and it would appear that the daily requirement of vitamin C in anacidity is about the same as that in other gastric diseases or in the normal state. That this is true is indicated by the report of Acharkan and Borinskaya,[72] who studied the maintenance of ascorbic acid saturation in patients with ulcer. These investigators found that no larger amounts were required to maintain saturation than in normal persons, and they noted at the same time that the amount of ascorbic acid in the gastric juice increases correspondingly to the increase of its concentration in the blood.

The measurement in situ of the p_H of the antral and pyloric portions of the stomach and the duodenum has been done by means of a special intragastric electrode. Breuhaus and Eyerly [73] have previously contrasted in situ p_H values with those obtained by aspiration and found that marked differences were not uncommon. The present investigation was aimed at a comparison of the in situ p_H values of the antrum of the stomach, pylorus and duodenum of normal subjects with those of patients with duodenal ulcer and achlorhydria. Normal persons and patients with ulcer had essentially the same fasting gastric p_H values and stimulation with histamine produced a lower gastric p_H in normal subjects than in patients with ulcer. The alternation of administration of an antacid with milk and cream feedings raised the p_H of the stomach, pylorus and duodenum more than half-hour feedings alone. In patients with achylia, the gastric reaction was mildly acid. Milk and cream feedings or a combination of such feedings with administration of antacids lowered the gastric and duodenal p_H of patients with pernicious anemia below that found in the fasting state. The duodenal reactions of normal persons and of patients with ulcer and with achylia tended to remain mildly acid. On the basis of these studies, the authors attempt to invoke an acid mechanism other than that of the secretion of hydrochloric acid, but it is quite possible that careful electrolyte studies of the gastric contents would not confirm their suggestion

70. Koehler, A. E., and Windsor, E.: The Effectiveness of Replacement Therapy in Achlorhydria, Ann. Int. Med. **18**:182, 1943.

71. Chernya, Y. M.: Vitamin C and the Secretory Insufficiency of the Stomach, Vopr. pitan. **10**:27, 1941.

72. Acharkan, A. I., and Borinskaya, E. N.: Study of C-Vitamin Balance in Ulcerous Patients, Vopr. pitan. **10**:22, 1941.

73. Breuhaus, H. C., and Eyerly, J. B.: In Situ p_H of the Antrum of the Stomach, Pylorus and Duodenum, Gastroenterology **1**:583, 1943.

that acid other than hydrochloric acid influences the p_H of the upper part of the gastrointestinal tract.

Studies of gastric secretion in the newborn infant are of some interest. Ritter [74] shows that the stomach of the newborn infant exhibits a high secretory capacity, with figures that suggest hypersecretion, as judged by adult standards. An appreciable number of infants in his study showed a lack of free hydrochloric acid, which he thinks may be a significant factor in the development of anemia and rickets in infants, in spite of an adequate intake of iron, calcium and vitamin C. Miller [75] carried out studies on secretion of gastric acid during the first year of life, and his studies confirmed Cutter's results, that there is a rapid increase in gastric acidity during the first year of life. Without histamine, he showed that there is a rapid increase in the concentration of gastric hydrochloric acid during the first twelve months, with a probable increase in volume, and at the end of this period the reaction of the stomach to a test meal closely resembles that of an adult. Accompanying the development of the digestive power of the stomach, there is a diminution in the number of achlorhydric infants.

Methods for studying digestive activity in the intestinal tract are time consuming and as a rule permit only approximate results. Studies by Berger and Oppenheim [76] on the drainage output from the human duodenum indicate that effective duodenal drainage can be achieved without the use of an obstructing balloon. This was accomplished by providing optimum suction, which permitted the removal of practically all of the secretion. Simultaneous drainage of the duodenum and jejunum under these conditions showed that the escape of fluid during an adequate duodenal drainage was negligible (0 to 4 per cent). Employment of this technic, if successful, would simplify the study of the collection of duodenal contents but would not preclude its dilution by gastric juice.

An ingenious method of determining the digestive activity in any portion of the human digestive tract is presented by Elsom and his associates.[77] The food substance to be digested is placed in a fenestrated metal cylinder that is housed in an outer cylinder which protects the contained material from the digestive tissues. The apparatus is introduced to any desired level of the digestive tract by intubation, and when desired the fenestrated cylinder is partially ejected from its housing by air pressure, the test substance thus being exposed to the intestinal juice. The amount of material lost by digestion in a measured period is determined chemically. A few illustrative results are given in the article, but the value of the method for studying digestive processes in various diseases awaits application.

The presence of alkaline phosphatase in the small intestine has been recognized for many years, but little attention has been paid to the phosphatase activity of the intestinal secretions. This particular phase of intestinal secretion was studied by Kosman and his associates [78] at various levels of the intestinal tract. The results of the studies indicated that the phosphatase activity of the duodenal,

74. Ritter, J. A.: Fractional Gastric Analysis in the Newborn: Preliminary Report, Pennsylvania M. J. **44**:1321, 1941.

75. Miller, R. A.: Gastric Acidity During the First Year of Life, Arch. Dis. Childhood **17**:198, 1942.

76. Berger, W. V., and Oppenheim, E.: Drainage Output from the Human Duodenum: Extrinsic Factors Influencing Drainage, Gastroenterology **1**:285, 1943.

77. Elsom, K. A.; Chornock, F. W., and Dickey, F. G.: A Method of Determining the Digestive Activity in any Portion of the Human Gastrointestinal Tract: Some Measurements of Protein Digestion in the Stomach and Small Intestine, J. Clin. Investigation **21**:795, 1942.

78. Kosman, A. J.; Kaulbersz, J. W., and Freeman, S.: The Secretion of Alkaline Phosphatase by the Dog's Intestine, Am. J. Physiol. **138**:236, 1943.

jejunal and ileal contents obtained from enterostomized dogs after various test meals showed the greatest activity after protein and fat meals and the least after a carbohydrate meal. Large quantities of phosphatase were obtained in the secretions of isolated intestinal loops. The degree of activity of various segments of the intestinal tract was diminished from above downward, the duodenum and jejunum containing the greatest concentration of phosphatase in the secretions and the colon the least. The distribution of alkaline phosphatase in the different parts of the alimentary tract, as shown by tissue stains, was studied by Bourne,[79] whose findings agree with the results obtained by other workers. In relation to the phenomenon of phosphorylation, he points out the important fact that the presence of phosphatase in the brush borders of cells in those parts of the alimentary tract where most active absorption can take place, i. e., the duodenum, jejunum and rectum, is in partial contrast to the absence of a reaction in the epithelial cells in those parts of the tract which are not important centers of absorption, i. e., the stomach and colon.

Absorptive Aspects.—The complex phenomenon of absorption from the gastrointestinal tract still includes many unexplained processes. Phosphorylation remains somewhat of a hypothesis, but continued studies contribute to its further elucidation. Iodoacetic acid, which prevents phosphorylation, has been reported to diminish absorption of the three hexoses, dextrose, fructose and galactose. Since iodoacetic acid is toxic, conclusions from such experiments have doubtful value. By the use of phlorhizin, more reliable deductions are possible, and studies on the organic phosphate and "fructose" in the rat intestinal mucosa as affected by dextrose and phlorhizin have been made by Beck.[80] Increases in nonpyrophosphate organic phosphorus in compounds reacting like fructose were much smaller in rats fed dextrose and phlorhizin than in rats fed dextrose only. No significant difference was found in pyrophosphate organic phosphate, and such a finding supports the position that active absorption of dextrose, fructose and galactose proceeds through phosphorylation.

Bellini and Cera [81] studied the behavior of the glycerophosphatases of the intestine during intestinal resorption of glycerophosphate. The glycerophosphatase content of the intestinal mucous membrane of fasting rats was determined, after which sodium glycerophosphate was injected into a section of the intestine which was tied off toward the stomach. Four hours after the injection the glycerophosphatase content of the intestinal mucous membrane had been reduced about 40 per cent, while at the same time the injected ester was hydrolyzed. The rate of absorption of dextrose from the intestine was studied in rats by Pauls and Drury [82] in the presence of diabetes. Depancreatized rats were used. Under such conditions, even on a high carbohydrate diet, the animals lost large amounts of dextrose daily in the urine and consumed correspondingly large amounts of food. The diabetic rats appeared to store sugar with difficulty and on a high carbohydrate diet consumed large amounts of sugar. Even assuming that the intestinal absorption of dextrose proceeded at the same rate throughout the day and night, the

79. Bourne, G.: The Distribution of Alkaline Phosphatase in Various Tissues, Quart. J. Exper. Physiol. **32**:1, 1943.

80. Beck, L. V.: Organic Phosphate and "Fructose" in Rat Intestinal Mucosa, as Affected by Glucose and by Phlorizin, J. Biol. Chem. **143**:403, 1942.

81. Bellini, L., and Cera, B.: The Behaviour of the Glycerophosphatases of the Intestine During Intestinal Resorption of Glycerophosphate, Biochim. e terap. sper. **27**:146, 1940.

82. Pauls, F., and Drury, D. R.: The Rate of Glucose Absorption from the Intestine of Diabetic Rats, Am. J. Physiol. **137**:242, 1942.

absorption coefficients were extremely high, indicating that the absorption mechanism of the intestinal tract under these circumstances operates efficiently.

The absorption of fat from the gastrointestinal tract was studied by Rekers, Abels and Rhoads.[83] The subjects studied included 2 normal persons and 1 patient with gastric cancer, 1 with a total gastrectomy, 1 with generalized atrophic gastritis and 2 with hepatic cirrhosis. An abnormal absorption of fat was demonstrated only in the gastrectomized patients and in the patient with atrophic gastritis. This is of interest as indicating that hepatic dysfunction apparently plays no constant significant role in the absorption of gastrointestinal fat. Fluoroscopic studies proved that increased intestinal motility was not a causative factor for the steatorrhea. The authors consider the possibility that the proper absorption of lipids is influenced by the presence of a normal functioning gastric mucosa, since both the patient with severe gastric atrophy and the one entirely lacking a stomach suffered from a decreased efficiency of fat absorption.

An attempt to illustrate absorption of fat is to be found in the experiments of van Weel,[84] who determined the distribution of dipeptidase and maltase in the small intestine by the use of histochemical micromethods. The distribution of dipeptidase indicated that a synthesis of this enzyme might occur in the cells of Paneth. Comparison of the results on enzymes in the duodenum and ileum in the small intestine of rats indicates a concentration of maltase in the crypts of Lieberkühn and secretion of the enzyme by the secretory cells. The author explains the resorption of fats by a splitting of the larger molecules into small particles and a resynthesis of the specific fats in the cells.

The interrelation of calcium and fat utilization in the growing rat was studied by French.[85] Balance experiments were conducted on young male rats, and with adequate synthetic diets the utilization of calcium decreased moderately and consistently in the order of the increasing fat content of the diets from 5 to 28 per cent and decreased considerably for the 45 per cent fat diet. The intestinal contents were more acid with the 5 per cent fat diet than with those richer in fat. The most efficient utilization of calcium accompanied the most acid reaction. At least two factors seemed to be involved in the physiologic relationship between fat and calcium utilization: (1) the acidity of the intestinal tract and (2) the formation of readily absorbable bile–fatty acid–calcium complexes.

By means of a perfusion method, Niimoto[86] determined the absorption of water in the ileum, ascending colon and rectum of rabbits, using 15 cm. lengths of intestine. The absorption averaged 11.5 cc. per hour in the ileum, 15.6 cc. per hour in the ascending colon and only 4.4 cc. per hour in the rectum. Various solutions of sodium chloride, sodium sulfate and magnesium sulfate showed no essential differences in their effects on water absorption, which depended essentially on the tonicity of the solutions. According to the degree of absorption of water by the small intestine, solutions of these salts can be arranged in the following decreasing order: sodium chloride, sodium sulfate and magnesium sulfate.

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83. Rekers, P. E.; Abels, J. C., and Rhoads, C. P.: Metabolic Studies in Patients with Gastrointestinal Cancer: IV. Fat Metabolism; a Method of Study, J. Clin. Investigation **22**:243, 1943.

84. van Weel, P. B.: Histophysiology of the Small Intestine: III. Changes in the Glands of the Small Intestine During Digestion and During the Absorption of Fat, Ztschr. f. Zellforsch. u. mikr. Anat. **29**:751, 1939.

85. French, C. E.: The Interrelation of Calcium and Fat Utilization in the Growing Albino Rat, J. Nutrition **23**:375, 1942.

86. Niimoto, I.: A Method for the Description of Intestinal Movements in Situ and Water Absorption in the Rabbit Intestine, Okayama-Igakkai-Zasshi **51**:1110, 1939.

Nicolai[87] found in earlier experiments that the absorption of phenol from the isolated jejunum of the rat showed a break in the time curve of the amount absorbed; i. e., at a certain point the amount of phenol in the intestine underwent a transitory increase instead of a decrease. This was interpreted as a protective function through which the poison was removed, even though only momentarily, from the body. In new experiments on animals whose jejunums had been irritated by the administration of castor oil and croton oil, this break in the curve was no longer evident, a finding that suggested a lowered protective function of the intestinal wall in the presence of an inflammatory process. Somewhat similar observations on the storage of indole in the intestinal wall following its absorption showed that in normal animals and in animals with an experimental fresh enteritis the initial storage of indole was about identical. The concentration in the intestinal wall, however, fell rather rapidly, reaching a zero value at the end of forty-five minutes, as compared with a constant value during sixty minutes in the normal animals. In a more chronic form of intestinal irritation, the amount stored in the intestinal wall reached a much lower initial level than in the normal animals or in those with a rather acute form of intestinal irritation and fell to zero within thirty minutes.

Dille and Whatmore[88] report data on the absorption of lanatoside C from the gastrointestinal tract of cats, comparing it with the absorption of tincture of digitalis. Lanatoside C is a crystalline glucoside isolated in mechanically pure form from digitalis lanata. The greatest absorption of lanatoside C and of tincture of digitalis U.S.P. XI takes place in the intestine, but quantities are also absorbed from the colon and stomach. The crystalline glucoside is absorbed more rapidly from the intestine than the tincture of digitalis. The studies show that partial destruction or inactivation of both substances takes place in the lumen of the gastrointestinal tract. Peterson and Finland[89] determined the absorption and excretion of a single dose of a sulfonamide drug in normal human subjects after oral and duodenal administration, and in addition, the effects of a meal, of the simultaneous administration of sodium bicarbonate and of the administration of a sulfonamide compound in the form of the sodium salt. A 5 Gm. dose of sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine was used. The fluid intake was kept at a constant level. It was found that sulfanilamide was absorbed rapidly and completely when given orally or into the duodenum. Food delayed absorption but did not diminish the amount excreted in the urine. Sulfapyridine, sulfathiazole and sulfadiazine were poorly absorbed from the duodenum, and sulfadiazine was absorbed more slowly when given after a meal than when given during fasting. Alkali appeared to increase the amount of the drug absorbed when given with sulfadiazine after a meal. Sodium bicarbonate hastens the absorption of sulfadiazine when given during fasting but does not increase the amount absorbed, and sodium sulfadiazine is rapidly absorbed from the duodenum or after oral administration in a fasting subject, but absorption is delayed and less complete if it is given after a meal.

87. Nicolai, H.: Quantitative Absorption Studies with Pure Intestinal Poisons: III. Phenol Absorption in the Small Intestine of Enteritic Rats, Klin. Wchnschr. **20**:80, 1941.

88. Dille, J. M., and Whatmore, G. B.: Gastrointestinal Absorption of Lanatoside C, J. Pharmacol. & Exper. Therap. **75**:350, 1942.

89. Peterson, O. L., and Finland, M.: The Effect of Food and Alkali on the Absorption and Excretion of Sulfonamide Drugs After Oral and Duodenal Administration, Am. J. M. Sc. **204**:581, 1942.

Factors affecting the absorption of sodium dl-mandelate from the intestine of cats were studied by Garry and Smith.[90] From the small intestine and from the colon in decerebrated cats, there was slight but unequivocal preferential absorption of the laevo form of mandelic acid. Such preferential absorbing power was not shown during ether or chloroform anesthesia, was absent from intestines kept alive in vitro, and did not survive in the intestines of cats recently killed. The selective absorbing power seemed to be associated with the integrity of the intestinal epithelium.

The selective absorption of botulinum toxin was studied by Dack and Hoskins.[91] Amounts of botulinum toxin type A which were lethal when fed to 2 monkeys were without effect when injected into the colons of 4 others. In a second experiment, large doses of toxin were injected into the colons of 3 surviving monkeys, and botulism developed in only 1. The fourth surviving monkey served as a control and was given toxin orally. It showed symptoms of botulism within twenty-four hours. A discussion of these results is given, concerning the relation of the permeability of the colon to toxin and the delayed symptoms sometimes occurring in patients with botulism.

Studies on the absorption of various iron preparations is to be found in a report by Labarre.[92] Iron apparently is absorbed by the capillary vessels of the intestinal mucosa, not by the lymphatics. It was found that better absorption of iron is obtained following the use of phosphogluconate of iron than from ferrous sulfate, pills of ferrous carbonate or iron and ammonium citrates. The greater absorption of this iron salt is due to the fact that it is very soluble in water, that it is combined in a bivalent state, and that a 2 per cent solution of the salt has a p_H of 6.2, which corresponds to the p_H of the duodenum, where most absorbable iron passes into circulation.

CLINICAL ASPECTS

Thoracic Pain and Disturbances in the Upper Part of the Digestive Tract.—The interpretation of pain arising from gastrointestinal lesions is sufficiently difficult to warrant attention to any articles contributing further light on the mechanism of its production and the course of its transmission. Harrison[93] discusses puzzling aspects of pain in the chest and describes in particular certain gastrointestinal conditions which may be sources of diagnostic error. The occasional occurrence of thoracic pain secondary to duodenal ulcer is illustrated by careful histories. This is a rather unusual manifestation, and Harrison emphasizes the diagnostic importance of the circumstances under which pain occurs, as well as the actual location where the pain is perceived. He mentions thoracic pain due to cascade stomach, which may produce an abnormal degree of spasm between the cardia and the body of the stomach, and in addition cites instances of angina-like pain secondary to diverticulum of the stomach. With the latter there seems to be no relation to effort but a definite relation to meals, and the clinical picture is not unlike that associated with esophageal hiatus hernia.

Alvarez[94] cites one of the important points made by Wolf and Wolff in regard to the production of gastric pain. Pain resulted from distention of the coats of

90. Garry, R. C., and Smith, I. A.: Factors Affecting Absorption of Sodium dl-Mandelate from the Intestine of Cats, J. Physiol. **101**:484, 1943.

91. Dack, G. M., and Hoskins, D.: Absorption of Botulinum Toxin Through the Colon of Macaca Mulatta, J. Infect. Dis. **71**:260, 1942.

92. Labarre, J.: Absorption and Hematinic Action of Ferrous Phosphogluconate Ferreux, Rev. canad. de biol. **1**:104, 1942.

93. Harrison, T. R.: Some Puzzling Aspects of Pain in the Chest, J. A. M. A. **120**:519 (Oct. 17) 1942.

94. The Production of Pain in the Stomach, editorial, Gastroenterology **1**:615, 1943.

the stomach or from the force of an unusually vigorous gastric contraction. Neither the threshold nor the intensity of the pain experienced was altered by varying the area of gastric wall stimulated. Pricking or pinching the mucosa or application of strong faradic stimuli or strong acid failed to cause pain, unless at the time the gastric mucous membrane was congested and edematous. The latter point in particular is of extreme importance and, as Alvarez points out, agrees with observations made years ago by Ivy. It may well explain why ulcers are sometimes painful and at other times not.

A partial anatomic explanation for the unusual distribution of pain arising from gastric stimulation may be found in the studies of Balchum and Weaver.[95] It is now generally recognized that esophageal or gastric pain may at times simulate that of angina pectoris, even to its radiation down the arm. Although the experiments of these investigators were performed on dogs and are therefore subject to a certain amount of skepticism, it is of extreme interest that objective signs of pain following distention of the stomach were shown to be independent of the vagus and phrenic nerves and of the anterior roots of the thoracic and lumbar spinal nerves. Evidence is presented which indicates that some of the visceral afferent fibers involved in the mediation of pain that follows distention of the stomach are contained within the greater splanchnic nerve. These fibers traverse the rami communicantes of the eighth through the thirteenth thoracic spinal nerve, entering the spinal cord through the corresponding posterior roots. Some of these fibers seem to traverse the sympathetic trunk as far cephalad as the fourth thoracic. If these findings are correct and are applicable to human beings, such an anatomic distribution would go far toward explaining the anginal distribution of gastric and esophageal pain.

A careful discussion of the differential diagnosis of angina pectoris, with special reference to esophageal spasm and coronary occlusion, is contained in an article by Wolferth and Edeiken.[96] The authors divide the differential diagnosis of angina pectoris into two parts: differentiation from seizures of noncardiac origin and differentiation from acute coronary occlusion. In their opinion, esophageal spasm is of major clinical importance. They state that with "anginal" pain due to esophageal spasm there is a history of difficulty in swallowing during an attack and glyceryl trinitrate fails to relieve the pain, which may respond to antispasmodics, sedatives and psychotherapy. The electrocardiogram is not altered during attacks. There are many who would disagree with the statement that glyceryl trinitrate does not relieve esophageal spasm and pain resulting therefrom, but it is true that as a rule a careful history will differentiate between the substernal pain due to coronary heart disease and that due to esophageal or gastric disorders. In this connection, it is proper to refer to an article by Levy and Boas,[97] who present for consideration angina pectoris and the syndrome of peptic ulcer. These authors point out that the symptoms of peptic ulcer and angina may occur suddenly and simultaneously, and occasionally acute peptic ulcer may be associated with coronary thrombosis. Repeated attacks of angina at rest, finally eventuating in coronary thrombosis, may occur two or three hours after meals and during the night,

95. Balchum, O. J., and Weaver, H. M.: Pathways for Pain from the Stomach of the Dog, Arch. Neurol. & Psychiat. **49**:739 (May) 1943.

96. Wolferth, C. C., and Edeiken, J.: The Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion, Pennsylvania M. J. **45**:579, 1942.

97. Levy, H., and Boas, E. P.: Angina Pectoris and the Syndrome of Peptic Ulcer, Arch. Int. Med. **71**:301 (March) 1943.

characteristic of pain from ulcer. When symptoms of angina and ulcer coexist, successful therapy for ulcer may cause remission of the anginal syndrome. The authors present 14 case histories and offer a detailed explanation of the phenomena just mentioned, which are largely based on the old theory of a vagovagal reflex. It should be stated that such instances are of extreme interest but are uncommon, inasmuch as the vast majority of patients with ulcer do not have associated coronary disease or coronary symptoms, as pointed out previously by White and his collaborators.

Esophagus,—Esophageal tumors which do not involve the mucosa are rare. Schatzki and Hawes [98] report a small group of intramural esophageal tumors and describe in detail the important diagnostic features to be noted by the roentgenologist. Gastrointestinal hemorrhage from esophageal polyps is extremely rare. Such an occurrence is described by Dickes and his associates,[99] who report a case of multiple polyps of the esophagus causing intermittent bleeding. Diagnostic proof rested on repeated esophagoscopic examinations. Pennes [100] adds a report of a case of leiomyosarcoma involving the middle and lower thirds of the esophagus to the 5 cases previously noted in the literature.

The incidence of successful esophageal surgical operation for malignant or benign tumors is still increasing, due largely to the results of transthoracic procedures. Interesting reports are those of Brock,[101] Franklin,[102] Allison [103] and Kay.[104] Although the technic of radical removal of esophageal cancer continues to improve, it is obvious that consideration must still be given to radiation therapy for this serious condition. Smithers and his associates [105] record the results of roentgen therapy in 44 patients with cancer of the esophagus. Thirty-two of the series had what was considered an adequate amount of therapy. Thirty of the entire group obtained some relief and 11 complete relief of symptoms. Three patients were still alive and free of symptoms at the end of six and one-fourth years, five years, and four and two-thirds years, respectively, after treatment.

Congenital atresia of the esophagus represents the most frequent type of congenital anomaly of this organ and consists of a blind upper esophageal segment and a lower segment communicating with the trachea. A series of instances of this anomaly are reported by Addey,[106] Chont and Starry [107] and Haight and

98. Schatzki, R., and Hawes, L. E.: The Roentgenological Appearance of Extramucosal Tumors of the Esophagus, Am. J. Roentgenol. **48**:1, 1942.

99. Dickes, R. R.; Knudsen, A. F., and Franco, S. C.: Multiple Polyps of the Esophagus: Report of a Case with Complicating Recurrent Gastrointestinal Hemorrhages, Arch. Int. Med. **70**:121 (July) 1942.

100. Pennes, A. E.: Leiomyosarcoma of the Esophagus, Am. J. Roentgenol. **48**:336, 1942.

101. Brock, R. C.: Cardio-Esophageal Resection for Tumor of the Cardia: Report of a Successful Case, Brit. J. Surg. **30**:146, 1942.

102. Franklin, R. H.: Two Cases of Successful Removal of the Thoracic Esophagus for Carcinoma, Brit. J. Surg. **30**:141, 1942.

103. Allison, P. R.: Report of Four Cases of Esophageal Carcinoma Treated by Excision, Brit. J. Surg. **30**:132, 1942.

104. Kay, E. B.: Experimental Observations on Reconstructive Intrathoracic Esophagogastric Anastomosis Following Resection of the Esophagus for Carcinoma, Surg., Gynec. & Obst. **76**:300, 1943.

105. Smithers, D. W.; Clarkson, J. R., and Strong, J. A.: The Roentgen Treatment of Cancer of the Esophagus, Am. J. Roentgenol. **49**:606, 1943.

106. Addey, W. A.: A Case of Congenital Atresia of the Esophagus, Brit. J. Radiol. **13**:179, 1940.

107. Chont, L. K., and Starry, L. J.: Congenital Atresia of the Esophagus: Report of Four Cases, Radiology **40**:169, 1943.

Towsley.[108] The last-mentioned report comments on the cases of 15 patients admitted to the University of Michigan Hospital during the past seven years. A detailed description of the first successful correction of the condition by operation is given. The authors note that since their paper was written 8 additional patients have been similarly treated, 4 of whom have been operated on successfully. The surgically ideal plan for the correction of this condition is a reconstruction of the continuity of the esophagus by an extrapleural ligation of the fistula and an end to end anastomosis of the esophageal segments. Another excellent example of modern surgical treatment is contained in a report by Davis and Stafford.[109] These authors describe the successful reconstruction of an extrathoracic esophagus in a child suffering from progressive esophageal stenosis secondary to the swallowing of concentrated lye, which finally resulted in complete obliteration of the esophagus from the neck to the stomach.

Diaphragmatic Hernia.—The increasing frequency of recognition and diagnosis of diaphragmatic hernia is pointed out by Harrington [110] in an excellent article on the roentgenologic aspects of this condition. Between 1908 and 1925, this diagnosis was made in 30 instances; from 1926 to 1941, the condition was diagnosed more than 600 times, and the author has operated on 295 patients. This definite increase in frequency of recognition is due primarily to the development of roentgenologic methods of diagnosis. On the basis of his extensive experience, Harrington discusses the roentgenologic and clinical considerations in the diagnosis of this condition, taking up nontraumatic and traumatic hernia, esophageal hiatus hernia, congenital short esophagus, dilatation of the lower end of the esophagus with relaxation of the cardia of the stomach, and congenital diaphragmatic hernia due to structural deficiencies of the diaphragm. An interesting statement is that it was found that an average of three previous erroneous clinical diagnoses had been made before a correct diagnosis was established. Indications for surgical intervention are given.

Sahler and Hampton [111] stress the fact that the incidence of hiatus hernia lesions is considerably higher than has been appreciated, and they direct attention toward the frequent occurrence of hemorrhage. An exact description of the roentgen findings associated with this condition is given. They properly conclude that if neither gastritis nor ulceration is present in the hernial lesion bleeding will not be encountered.

An unusual symptom secondary to hiatus hernia is reported by Stubenbord [112]—namely, paroxysmal auricular fibrillation. Attacks of this arrhythmia were precipitated by overindulgence in alcohol or food or by worry and fatigue. Although the association of paroxysms of fibrillation with the hiatus hernia may have been only incidental, the report is of interest. A more unusual complication of diaphragmatic hernia is that reported by Deaner and his associates,[113] who present the

108. Haight, C., and Towsley, H. A.: Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula: Extrapleural Ligation of Fistula and End-to-End Anastomosis of Esophageal Segments, Surg., Gynec. & Obst. **76**:672, 1943.

109. Davis, J. S., and Stafford, E. S.: Successful Construction of an Extrathoracic Esophagus, Bull. Johns Hopkins Hosp. **71**:191, 1942.

110. Harrington, S. W.: Roentgenologic Considerations in the Diagnosis and Treatment of Diaphragmatic Hernia, Am. J. Roentgenol. **49**:185, 1943.

111. Sahler, O. D., and Hampton, A. O.: Bleeding in Hiatus Hernia, Am. J. Roentgenol. **49**:433, 1943.

112. Stubenbord, W. D.: Paroxysmal Auricular Fibrillation in Association with Hiatus Hernia: Report of a Case, Ann. Int. Med. **18**:406, 1943.

113. Deaner, S.; McMenemey, W. H., and Smith, S. M.: Haemothorax Due to Strangulated Diaphragmatic Hernia, Brit. M. J. **1**:72, 1943.

case of a 37 year old man who died two days after sudden onset of severe abdominal pain. The autopsy showed a hemothorax and, in addition, a loop of gangrenous stomach which had herniated through the diaphragm with a portion of the omentum.

Gastritis.—The literature on gastritis continues to grow. Much of it is controversial, and for this reason the extraordinary observations of Wolf and Wolff,[2] already referred to, are extremely pertinent. These investigators studied a subject with a permanent gastric fistula, and a recent report deals with an investigation of changes in the appearance in the gastric mucosa in this person after various stimuli. Several experienced gastroscopists have expressed doubt as to whether the changes in color and the appearance of localized spots on the lining of the stomach represent disease or "gastritis," or whether they should be looked on as within the limits of normal. Wolf and Wolff considered that the small hemorrhagic lesions and so-called "pigment spots" regarded by many as signs of disease are in reality artefacts due to the trauma of the gastroscope itself or to the suction applied to the wall by the stomach tube in making the preliminary gastric analysis. They state that many of the signs of "gastritis" may be encountered in the normally functioning stomach or may be produced therein by minor traumas associated with instrumentation. In their patient the healthy gastric mucosa varied in appearance within a wide range. When the rate of production of acid by the parietal cells was relatively slow, the mucosa was always comparatively pale, and in this state it was relatively resistant to injury unless the continuity of its protective covering of mucus was interrupted. Accelerated production of acid and motor activity were always accompanied by hyperemia and mucosal engorgement. When vascular engorgement was prolonged, the rugae became intensely red, thick and turgid, presenting the picture of what has been called "hypertrophic gastritis." In this state the mucosa was unusually fragile, hemorrhages and small erosion resulting from even the most minor trauma. Lowering of the pain threshold occurred, and symptoms were often associated with this condition. Thus, the difference between hyperfunctioning of the stomach and "hypertrophic gastritis" was seen to be mainly one of degree. Continued exposure of a small erosion to the digestive action of gastric juice for four days resulted in a peptic ulcer. In this connection, reference has already been made to the observations of Wolf and Wolff on changes in gastroduodenal blood flow. As already noted, they observed that accelerations in blood flow in the mucosa of the stomach were associated with gastric motor activity, histamine stimulation and various psychologic stimuli.

The significance of hemorrhagic or pigment spots as observed by gastroscopy has received further consideration by Ruffin and Brown.[114] On the basis of a large number of control gastroscopies, with or without operation, these authors are in agreement with the conclusions already alluded to, that hemorrhagic or pigment spots in the gastric mucosa can be produced by aspiration of the stomach and may occur in healthy persons. They feel that such lesions probably have no clinical significance.

A study of 40 healthy volunteers by Fitzgibbon and Long [115] throws still further doubt on the wisdom of uncontrolled diagnoses of hypertrophic gastritis. Two of their 40 subjects showed definite hypertrophic changes although symptoms were completely absent. They make the obvious suggestion that a large series of normal

114. Ruffin, J. M., and Brown, I. W., Jr.: The Significance of Hemorrhagic or Pigment Spots as Observed by Gastroscopy, Am. J. Digest. Dis. **10**:60, 1943.

115. Fitzgibbon, J. H., and Long, G. B.: A Gastroscopic Study of Healthy Individuals: A Preliminary Report, Gastroenterology **1**:67, 1943.

persons should be examined before one attempts to evaluate minor "hypertrophic" changes in the gastric mucosa.

Hebbel [116] has attempted to correlate the occurrence of gastritis with the appearance of gastric and duodenal ulcer and gastric carcinoma by means of autopsy and surgical specimens. The control group of specimens consisted of stomachs examined at autopsy of 260 persons free of manifest gastric disease. Certain findings are of interest: Gastritis was rarely encountered below the age of 30, and the majority of the stomachs reexamined were free of any significant change. Atrophic changes appeared only twice in persons under the age of 50. One hundred and eight specimens were from patients over 50 years of age, and of these 30 per cent showed gastric atrophy. These findings lend credence to the view that "atrophic" gastritis is in part, at any rate, the result of an aging or degenerative process, and they suggest the obvious need for a gastroscopic study of a much greater number of normal persons in various age groups. Examination of surgical material from stomachs excised for ulcer or carcinoma supported the frequently reported constancy of gastritis associated with ulcer. The author feels that there is good evidence that the process is primary and not secondary to ulcer and must be separated from the processes leading to atrophy and achlorhydria, in which the body is regularly involved. Changes in the body mucosa were rare in the group with duodenal ulcer and common in the group with gastric ulcer. There was in the series no evidence that carcinoma of the stomach arises with unusual frequency at the site of already diffuse atrophic gastritis.

Maher and his associates [117] have reviewed their experiences based on gastroscopic and histologic examinations of 40 patients with peptic ulcer. On the basis of their observations they state that the gastritis associated with peptic ulcer is largely similar to that seen in patients with gastric cancer, a fact that strongly suggests that the gastritis per se may not be a specific precursor of either gastric cancer or peptic ulcer. They stress the frequent presence of microscopic evidence of atrophic gastritis in stomachs which appear normal gastroscopically as indicating the necessity for further study of control groups of stomachs.

The value of gastroscopy in the diagnosis of gastric tumor is thoroughly presented by Schindler and Letendre.[118] Among 95 cases of gastric tumor proved by operation, the lesion was not seen in 5 cases of gastric cancer, and in 5 others an incorrect gastroscopic interpretation was made. Sarcoma was mistaken for polyposis once, and a benign mucosal tumor was called malignant in 1 instance. In 3 cases, however, gastroscopic examination revealed a tumor not palpated or seen by the surgeon at laparotomy but found later in the resected specimens. There were 15 diagnostic failures on the first roentgen examination.

That clinical symptoms vary tremendously in patients showing chronic gastritis on gastroscopy is a fact receiving confirmation in various reports. Jackson and his associates [119] stress this fact in a review of over 1,000 gastroscopic studies. In 75 per cent of the patients pain was present, but as a rule there was no particular relationship to the ingestion of food and the duration of the pain was variable. Anorexia, indifference to food or fear of eating was noted in 45 per cent

116. Hebbel, R.: Chronic Gastritis: Its Relation to Gastric and Duodenal Ulcer and to Gastric Carcinoma, Am. J. Path. **19**:43, 1943.

117. Maher, M. M.; Zinninger, M. M.; Schiff, L., and Shapiro, N.: Some Observations on Gastritis and Peptic Ulcer, Am. J. M. Sc. **205**:328, 1943.

118. Schindler, R., and Letendre, P.: Analysis of Relationship of Surgery and Gastroscopy in Ninety-Five Cases of Gastric Tumor, Surg., Gynec. & Obst. **75**:547, 1942.

119. Jackson, C. L.; Swalm, W. A., and Morrison, L. M.: Diagnosis and Treatment of Chronic Gastritis, Rev. Gastroenterol. **9**:193, 1942.

of the patients, with loss of weight, weakness and nervousness in an important number. Nausea and vomiting were present in over one fifth of the patients, and constipation or diarrhea in 40 per cent. It would seem that the atypical and varying histories of patients with gastritis are in themselves a suggestive feature of this condition, but an accurate diagnosis cannot be based on the history alone. These authors advocate the obtaining of a biopsy specimen of gastric mucosa through an open tube gastroscope for an accurate evaluation of the underlying condition, and they claim satisfactory results by this method.

Hardt and his associates [120] examined gastroscopically 119 patients with pulmonary tuberculosis with gastrointestinal symptoms. Atrophic changes in the gastric mucosa were noted frequently in far advanced pulmonary tuberculosis, and the authors state that the histopathologic picture indicates that these atrophic changes were primary, with secondary inflammatory changes. The comment of Ruffin in this connection is pertinent. He expressed the conviction that atrophy of the gastric mucosa in pulmonary tuberculosis is probably merely a local manifestation of a general condition, not primary gastritis at all but a degenerative process due to inadequate nutrition or actual vitamin deficiency. Flexner and Baum [121] also observed chronic superficial gastritis and gastric atrophy in an unusually large number of tuberculous patients. They could not correlate the abnormalities of the gastric mucosa, however, with the duration, severity or type of tuberculosis. Gastric symptoms failed to follow directly the gastroscopically demonstrated lesions, and this was thought to be influenced by rest in bed, the reduction in food consumption caused by anorexia and the frequent presence of achlorhydria. Browne, McHardy and Wilen [122] made gastroscopic examinations of 50 tuberculous patients and found a normal mucosa in only one third of them. They state, however, that no gastritis of pathognomonic significance was established. In order to study further the problem of gastric symptoms in tuberculous patients, these investigators attempted to produce tuberculous lesions in the pyloric segment of the dog by local inoculation with living tubercle bacilli. The results indicated that the submucosal and hematogenous routes were the only successful methods of exciting a significant mucosal change. The authors hope to produce and endoscopically observe the development of mucosal changes of tuberculosis in animals for comparison with similar lesions in human beings.

A curious diffuse metaplastic gastritis in a patient with prolonged cachexia and macrocytic anemia is recorded by Sailer.[123] Diffuse areas of squamous metaplasia, regardless of the causative factors, have hitherto not been described in the gastric mucosa. He reports such changes proved by autopsy and diagnosed by gastroscopy as atrophic gastritis. No apparent cause for the gastric changes were found, but a deficiency of vitamin A was suggested as a possible etiologic factor.

Atrophy of the gastric mucosa was diagnosed positively in 10 of 11 cases of hypothyroidism and myxedema by Golding.[124] Such a finding is further evidence

120. Hardt, L. L.; Weissman, M., and Coulter, J. S.: Gastric Atrophy in Far Advanced Pulmonary Tuberculosis Complicated by Intestinal Tuberculosis, Am. J. Digest. Dis. **9**:404, 1942.

121. Flexner, J., and Baum, O.: Gastroscopic Observations in Pulmonary Tuberculosis, Am. J. M. Sc. **204**:101, 1942.

122. Browne, D. C.; McHardy, G., and Wilen, C.: Gastric Mucosal Changes of Tuberculosis, Am. J. Digest. Dis. **9**:407, 1942.

123. Sailer, S.: Diffuse Metaplastic Gastritis in a Patient with Prolonged Cachexia and Macrocytic Anemia, Arch. Path. **35**:730 (May) 1943.

124. Golding, F. C.: The Association of Atrophic Gastritis with Hypothyroidism: A Preliminary Report of Eleven Cases, Ann. Int. Med. **17**:828, 1942.

that gastric atrophy is frequently an expression of some form of deficiency disease, in this particular instance a deficiency of thyroid secretion or a nutritional deficiency secondary to the primary myxedema.

Further studies on the gastric symptoms encountered in chronic alcoholism are presented by Gray.[125] Gastroscopic examinations were made on 100 chronic alcoholic addicts taken at random, with ages varying from 24 to 66. These men had been drinking from 1 to 6 pints (0.5 to 3 liters) of alcoholic beverages daily for from three to fifty-two years. The alcohol consumed included everything from wine to hair tonic. Normal gastric mucosa was observed in 55 patients who had had an average daily alcohol consumption of 3 pints (1.5 liters) for more than twenty-one years. Various forms of gastritis were noted in the remainder, 22 of whom showed superficial gastritis of varying degrees; 13 showed atrophy; and 8 showed a combination of superficial and atrophic gastritis. Only 4 of the 55 patients with normal stomachs had subjective complaints, whereas 24 of the 45 patients with chronic gastritis presented definite symptoms.

Schindler[126] states categorically on the basis of his wide experience that gastritis as a disease has a well established histopathologic picture, that it can be diagnosed reliably by gastroscopy and that therefore it can produce symptoms. Few would disagree with this last statement, although there can be little doubt that innumerable patients showing marked changes in the gastric mucosa have few, if any, symptoms.

As already suggested in some of the preceding papers, no characteristic clinical syndrome is typical of any form of gastritis. Pollard and Cooper[127] studied 50 patients showing the characteristics of hypertrophic gastritis; they feel that the diagnosis can be made only by exclusion and by gastroscopy, and not on the basis of clinical symptoms. Although admitting that gastritis can cause symptoms, Tumen and Lieberthal[128] conclude that the presence of gastritis did not regularly influence the clinical course of duodenal ulcer in a carefully studied group of 50 patients with this disease. Thirty-three of the patients with ulcer were shown by gastroscopy to have changes consistent with chronic gastritis. These changes were variable in type, and 16 patients showed normal gastric mucosa, as far as could be determined. A careful analysis of the patients' symptoms led to the conclusion that in individual cases it was possible that the gastritis might have added to the severity of the symptoms but that it often existed in an apparently symptomless manner. It was impossible to postulate the presence or absence of associated gastritis on the basis of the nature of the symptoms or the character of the response to treatment. An excellent clinical evaluation of chronic nonspecific gastritis is to be found in a general article by Eustermann,[129] who states that simulation of the ulcer symptom complex or hemorrhage, or both, is a frequent manifestation of hypertrophic, erosive or ulcerative gastritis; on the other hand, that gastritis in its various forms is often symptomless. He stresses the fact that chronic gastritis is generally refractory to treatment.

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125. Gray, S.: Epigastric Symptoms in Alcoholics With and Without Gastritis, Gastroenterology **1**:221, 1943.

126. Schindler, R.: On Chronic Epigastric Distress and Its Role in Chronic Gastritis: An Analysis of the Problem, Gastroenterology **1**:44, 1943.

127. Pollard, H. M., and Cooper, R. R.: Is There a Clinical Syndrome Characteristic of Hypertrophic Gastritis? J. Michigan M. Soc. **41**:473, 1942.

128. Tumen, H. J., and Lieberthal, M. M.: The Significance of the Gastroscopic Findings in Patients with Duodenal Ulcer, Gastroenterology **1**:555, 1943.

129. Eustermann, G. B.: Chronic Nonspecific Gastritis: Significance as a Clinical Entity, Gastroenterology **1**:54, 1943.

Benedict [130] analyzes 117 cases of hypertrophic gastritis without other gastric or duodenal pathologic change. Two thirds of the patients were males, and the most frequent symptoms were pain and vomiting. No relationship was found between the severity of the pain and the activity of the gastritis as observed endoscopically. The relation of pain to the ingestion of food and its relief by food or alkali were variable, but the history and course were like those of ulcer in an important number of instances. Hemorrhage occurred in 49 cases, with hematemesis in 31. Although no specific treatment was effective, two thirds of the patients were definitely relieved by the use of a bland diet, belladonna, and alkali or hydrochloric acid. Benedict believes that clinical improvement in most cases was definitely correlated with improvement in the appearance of the gastric mucosa.

Hurst [131] comments on a specific cause of gastritis and hemorrhage, the use of acetylsalicylic acid. He makes the interesting statement that from his experience in hospital and private practice since 1939, he would expect to obtain a history of this drug as a direct cause of hemorrhage in at least one half of 58 cases in which chronic ulcer, cancer and cirrhosis could be excluded. He stresses the importance of administering acetylsalicylic acid immediately after meals in order to avoid gastric irritation. (The gastroscopic appearance of this type of irritation has been well described.) An interesting addition to the technic of gastroscopy is reported by Robinson.[132] Fluorescein was used topically on the mucous membrane of the stomach by instillation through a tube. Gastroscopy was then done in a series of cases. Four cases with positive findings are reported to demonstrate that this procedure was helpful in visualizing superficial ulcers of the stomach. The dye aids in outlining and demonstrating the ulcer, giving a more accurate estimate of the diameter of the ulceration.

Esophageal perforation during gastroscopy is rare. An unusual instance is reported by Paul and Lage.[133] Four hours after gastroscopy their patient complained of pain in the throat and difficulty in swallowing, and two hours later he had a chill with a rise in temperature. The patient died twenty-four hours after gastroscopy. At autopsy, no explanation could be found for the accident, and even when air was blown into the esophagus no perforation could be discovered. A fibrinous, acute, phlegmonous cellulitis with extreme edema was found in the upper part of the thorax, however, and a minute perforation must have occurred. The relatively slight danger associated with gastroscopy is indicated by the fact that Benedict [134] records only 3 perforations in 1,507 gastroscopies. In each instance the perforation was through the wall of the stomach, and death occurred only once.

Experimental Ulcer.—Berk and his associates [135] have attempted to study in human beings and in animals the acidity of the ulcer-bearing area of the duodenum.

130. Benedict, E. B.: Hypertrophic Gastritis: Gastroscopic and Clinical Studies, Gastroenterology **1**:62, 1943.

131. Hurst, A.: Aspirin and Gastric Hemorrhage, Brit. M. J. **1**:768, 1943.

132. Robinson, H. M.: Fluorescein—An Aid in Gastroscopy, Am. J. Digest. Dis. **10**:181, 1943.

133. Paul, W. D., and Lage, R. H.: Perforation of Esophagus Caused by Flexible Gastroscope: Report of Case with Autopsy, J. A. M. A. **122**:596 (June 26) 1943.

134. Benedict, E. B.: Personal communication to the author.

135. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: The Effect of Ulcer on Acidity and Neutralizing Ability in Duodenal Bulb, Arch. Int. Med. **70**:959 (Dec.) 1942; The Acidity of the "Ulcer-Bearing Area" of the Duodenum in Normal Persons, Am. J. Digest. Dis. **9**:276, 1942; Duodenal Bulb Acidity Under Fasting Conditions in Patients with Duodenal

(Footnote continued on next page)

The reaction of this portion of the duodenum has received scant attention. In normal subjects, these investigators found that the important ulcer-bearing first portion of the duodenum is an acid area, with an average p_H in the fasting state of about 5.6 and after an Ewald meal of 5.0. Free acid is usually but not constantly absent. The duodenal bulb seems to be endowed with a capacity to neutralize, buffer and dilute the gastric chyme that generally exceeds the physiologic needs. None of the customary measures of gastric acidity in normal subjects can be used as a reliable index of the behavior of corresponding effective acidity (p_H) of the contents of the duodenal bulb. These authors conclude that in patients with duodenal ulcer, under fasting conditions the contents of the first part of the duodenum are more acid than in normal subjects, with an average p_H of 3.9. During fasting, free acid is found more often in the first part of the duodenum in these patients than in normal persons; free acidity when present tends to persist for longer periods. The ability of the duodenal bulb to neutralize, buffer and dilute gastric secretions in patients with ulcer is impaired but not wholly lost. This is considered to be due to gastric hypersecretion and to a defective neutralizing capacity in the duodenal bulb as well. Fasting normal dogs display a greater neutralizing power in the duodenal bulb then do normal men, and the authors suggest that this may be due to the fact that dogs rarely, if ever, display a spontaneous duodenal ulcer.

The importance of acid in the genesis of ulcer receives additional confirmation in the experiments of Hay and his associates.[136] These investigators produced maximal secretion of hydrochloric acid from gastric pouches of dogs by embedding histamine in beeswax and injecting it intramuscularly to permit gradual liberation of the drug. With the employment of this agent, gastric and duodenal ulcers may be produced with some regularity in a number of laboratory animals. Their results are confirmatory of work previously reported by Varco.

Cheney[137] continues to report on gastric ulcers in chicks due to dietary deficiencies. Cinchophen gastric ulcers may also be produced in chicks but may be prevented or modified by a dietary factor. The fact that certain bile acids and salts prevent the development of deficiency ulcers in chicks and may have a similar action against experimental cinchophen ulcers the author explains by assuming that bile promotes the intestinal absorption of a fat-soluble ulcer-preventive factor, designated as vitamin U. He suggests that the ulcer-producing properties of cinchophen are due not to direct action on the lining of the stomach but to an indirect effect on the liver, which, in turn, may interfere with the elaboration and storage of the antiulcer factor and its delivery to the wall of the stomach. Some comparable explanation may be evoked in those cases of ulcer occasionally seen in connection with cirrhosis of the liver and mentioned in previous years by Ask-Upmark. Other possible dietary factors are suggested in the report by Sharpless,[138] in which he describes hyperplasia and ulceration of the forestomach epithelium in rats in association with a deficiency of cystine, riboflavin, pyridoxine or choline. Sodium taurocholate or pepsin and hydrochloric acid increased the incidence of lesions in animals fed the poor diets. In

Ulcer, Arch. Surg. **45**:406 (Sept.) 1942; Duodenal Bulb ("Ulcer Bearing Area") Acidity in Fasting Normal People, J. Clin. & Lab. Med. **27**:1501, 1942.

136. Hay, L. J.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: Experimental Production of Gastric and Duodenal Ulcers in Laboratory Animals by the Intramuscular Injection of Histamine in Beeswax, Surg., Gynec. & Obst. **75**:170, 1942.

137. Cheney, G.: Cinchophen Gastric Ulcers in Chicks, Arch. Int. Med. **70**:532 (Oct.) 1942.

138. Sharpless, G. R.: Diet and Epithelial Hyperplasia in the Forestomach of Rats and Mice, Cancer Research **3**:108, 1943.

experiments on rats, Zucker and Berg [139] noted that diets adequate for excellent growth in all respects will lead to a high incidence of predominantly antral lesions if calcium is omitted from the salt mixture. Vitamin D deficiency plays no role.

Experimental acute gastric ulcers were produced in mice and in guinea pigs by Weedon [140] by exposure to sulfur dioxide gas. With minor concentrations of the gas only gastric distention was noted, but when the concentration was increased distention occurred at an earlier date and multiple hemorrhagic ulcers with perforations were frequent.

Protection against experimental ulcers has been obtained by various procedures. The survival time of dogs in which histamine was used to produce peptic ulcers was increased by Shock and Fogelson [141] by daily feeding of 0.5 Gm. of a fatty alcohol sulfate (Dreft). This denaturant inactivated the pepsin of the gastric juice and thus decreased its digestive powers. The application of this principle to human beings has not yet been proved of practical value.

Hands and his collaborators [142] have previously reported that enterogastrone depresses the motor and secretory activity of the stomach, and in an effort to determine its effect on Mann-Williamson ulcers they treated a series of 25 such ulcers in dogs. Control animals treated intravenously with an extract of pork muscle died of jejunal ulcer in four to thirty weeks, the average postoperative survival time being just under sixteen weeks. The muscle extract did not inhibit gastric secretion or motility. Of the dogs given injections of enterogastrone, jejunal ulcers developed in only 6. Eight of the 25 animals died within nine months without ulcer, living an average of nineteen weeks following operation. Eleven dogs were still alive without ulcer for more than nine months, and 7 of these for more than one year. Five of the latter 7 had been without treatment for from four to five months without ulcer developing. The authors are of the opinion that enterogastrone extract, even though as yet impure, has a remarkable potency in preventing jejunal ulcer in Mann-Williamson dogs. Analogous experiments were carried out by Beaver and his collaborators [143] on standard Mann-Williamson dogs. In all, 142 animals were employed, of which 42 were treated with an extract of urine of pregnant women, 42 with an extract of urine of normal women, and 30 with an extract of urine of patients having active symptoms of duodenal ulcer. The untreated dogs died within an average of seventy-one days. Of those treated with the extract of urine of pregnant women, 85 per cent of the animals were benefited. Of those treated with the extract of urine of normal women, 62 per cent were benefited. Only 24 per cent of the 30 dogs treated with the urine of patients with ulcer were benefited. Experimental results with extracts of urine of normal men are not complete, but the authors believe that the urine of normal men contains much less of the protective substance than the urine of normal women, though more than the urine of patients having active symptoms of ulcer. They believe that this protective substance is closely related to the gonadotropic hormone found

139. Zucker, T. F., and Berg, B. N.: Calcium Deficiency and Gastric Lesions in the Rat, Proc. Soc. Exper. Biol. & Med. **53**:34, 1943.

140. Weedon, F. R.: Experimental Acute Gastric Ulcer Produced in Animals by Exposure to Sulfur Dioxide Gas, New York State J. Med. **42**:620, 1942.

141. Shock, D., and Fogelson, S. J.: The Effect of a Protein Denaturant on Histamine Ulcers, Quart. Bull., Northwestern Univ. M. School **16**:142, 1942.

142. Hands, A. P.; Greengard, H.; Preston, F. W.; Fauley, G. B., and Ivy, A. C.: Prevention of Experimental Gastrojejunal Ulcer by Enterogastrone Therapy, Endocrinology **30**:905, 1942.

143. Beaver, D. C.; Sandweiss, D. J.; Saltzstein, H. C.; Farbman, A. A., and Sanders, A. W.: The Effect of Urine Extracts on the Prevention and Healing of Experimental Ulcers in Dogs, Am. J. Clin. Path. **12**:617, 1942.

in the urine of pregnant women and that its effect is not due to inhibition of gastric secretion or acid in the Mann-Williamson ulcers. Microscopically, the beneficial effect is shown by fibroblastic proliferation, new formation of blood vessels and epithelization of the mucosa.

Friedman and Podolsky [144] investigated the possibility that tissue proliferation at the site of experimental ulcers in urine-treated animals might be due to anterior pituitary substance with high prolactin activity. Experiments were carried out in pigeons, and on the fifth day after injection the crops were examined for increase in weight and for proliferation of the crop glands as suggested by McShan and Turner in 1937. Extracts of urine from pregnant and from nonpregnant women were used. None of the treated birds showed a gain in crop weight, although unmistakable evidences of crop proliferation were found in 1 bird of the control series and in none of the urine-treated series. The conclusion was reached that urine extracts which can cause fibroblastic proliferation and epithelization of the experimental ulcer do not do so because of prolactin. The results were suggestive but not conclusive, inasmuch as the extract employed did not have a high content of prolactin.

Clinical Ulcer.—Demonstration of gastric ulcerations in cases of diaphragmatic hernia is not too common. Rude [145] describes the clinical aspects of the condition and gives in detail important roentgenologic findings. The condition is best demonstrated with the patient recumbent in the Trendelenburg position with the body turned on the left side. Huber and Andreson [146] report a small series of interesting cases in which a gastric or duodenal ulcer was associated with similar lesions in the lower end of the esophagus or in the cardia. Ulcerations were demonstrated in cases of hiatus hernia, esophageal diverticulum and megaesophagus.

An uncommon site of primary ulceration is the jejunum. Dowdle [147] reports the case of a patient with chronic dilatation of the duodenum produced by obstructive, multiple jejunal ulcers. Nine additional cases have appeared in the literature, and in most instances the ulcers were found in the proximal portion of the jejunum opposite the mesenteric attachment.

The occurrence of recent acute peptic ulcer in the sixth and later decades of life is not particularly uncommon, but the report of Meyer and Saphir [148] is of some interest. Sixteen patients are reported on, the youngest being 60 years of age and the oldest 83. A clinical diagnosis was made for 5 patients. The fact that for the 11 other patients the diagnosis was not correctly made may have been due in part to the fact that an atypical history was obtained. This is particularly likely to occur with patients of this age group, in whom the threshold of pain perception is distinctly higher than in younger persons. As was to have been expected, microscopic changes in the region of the ulcer showed arterial changes that were definitely more severe than those noted in younger patients. Surgical operation on such patients, performed for perforation or because of the possibility

144. Friedman, M. H. F., and Podolsky, H. M.: Prolactin and Healing of Experimental Peptic Ulcer, Endocrinology **31**:689, 1942.

145. Rude, J. C.: Healed Gastric Ulcer with Associated Inflammatory Fibrotic Changes in a Diaphragmatic Hernia, Radiology **38**:729, 1942.

146. Huber, F., and Andreson, L. H.: Gastric and Duodenal Ulcer Associated with Lesions of the Lower End of the Esophagus and the Cardia of the Stomach, Am. J. Roentgenol. **48**:158, 1942.

147. Dowdle, E.: Multiple Primary Nonspecific Jejunal Ulcers with Chronic Duodenal Dilatation, Ann. Surg. **116**:348, 1942.

148. Meyer, J., and Saphir, O.: Peptic Ulcer in the Aged: A Clinical and Postmortem Study, Am. J. Digest. Dis. **10**:28, 1943.

of carcinoma, is not contraindicated because of age alone. A case of ulcer in a person of extreme age is reported by Tanner.[149] This patient died of perforation of a duodenal ulcer at the age of 91. Histologic examination showed a typical chronic duodenal ulcer.

That vascular changes may frequently complicate the problem of ulcer is indicated in an article by Schenken and his associates.[150] The average patient with ulcer, even in the later decades of life, has a relatively low blood pressure. These authors, in a review of the postmortem examinations of patients with gastric or duodenal ulcer, were impressed by the high incidence of hypertension and pancreatic erosion in those patients who died of massive hemorrhage. Of a group of patients who died of hemorrhage, nearly 60 per cent had hypertension and 75 per cent of the group had either hypertension or erosion of the pancreas or both. These findings indicate the cause of the increased mortality from hemorrhage in older patients with ulcer.

Variations in the percentage incidence of gastric and of duodenal ulcer continue to appear in various parts of the world. A recent report from Australia by Cleland,[151] based on postmortem examinations, shows that of 207 active or healed ulcers 60 per cent were gastric. There had been no change in the relative incidence of gastric and duodenal ulcers over a period of twenty-two years. In persons less than 50 years of age the incidence of gastric and that of duodenal ulcers were about equal; after that age there was a rapid increase in the incidence of gastric over duodenal ulcers.

The infrequency with which ulcer occurs in Southern Negroes has been mentioned on numerous occasions, and an article by Finney[152] again stresses this point in an analysis of cases of ulcer in Alabama. Whether the incidence in Negroes will increase under war conditions and with increased industrialization of the South will be a matter for interesting speculation. A report from southwest India by Somervell[153] covers his experience with 4,000 patients operated on during the past twenty years. In a former paper he pointed out that peptic ulcer in this part of India seemed chiefly due to deficient diet, the greatest deficiency possibly being that of vitamin A. In the present report he states that an extensive study of the vitamin situation in southwestern India showed that vitamins A and B_2 are noticeably lacking and, in addition, that there is an overwhelming preponderance of carbohydrates in the diets, with relatively little protein and fat, a condition which appears to increase gastric acidity. He destroys one of the time-honored colonial traditions in stating that the eating of curry has little to do with ulcer, since in parts of India where ulcer is relatively uncommon, even hotter curry is eaten than in other parts of the country. One point that may be questioned in his report is the statement that rapid reduction of gastric acidity is obtained by the ligature of a sufficient number of arteries in the wall of the stomach; in view of recent experimental evidence, such a statement can hardly be convincing.

The relatively high incidence (approximately 10 per cent) of peptic ulcer in association with polycythemia has been known since 1905. Statistically, the

149. Tanner, N. C.: Gastroduodenal Surgery in the Aged, Brit. M. J. **1**:563, 1943.

150. Schenken, J. R.; Burns, E. E., and Maes, U.: The Role of Hypertension and Pancreatic Erosion in Massive Hemorrhage from Gastric and Duodenal Ulcers, Surg., Gynec. & Obst. **74**:1058, 1942.

151. Cleland, J. B.: Gastric and Duodenal Ulcers in South Australia, M. J. Australia **2**:295, 1942.

152. Finney, J. O.: Peptic Ulcer: An Analysis of One Hundred and Eighty-Eight Cases with Special Reference to Hemorrhage, J. M. A. Alabama **12**:73, 1942.

153. Somervell, T. H.: Further Contributions to the Causation and Treatment of Duodenal Ulcer and Its Complications, Brit. J. Surg. **30**:113, 1942.

record of 163 cases of polycythemia vera by Tinney and his associates [154] is of interest. Eleven of the patients were definitely shown to have ulcer, and 5 others gave a typical history and had had a diagnosis of ulcer made elsewhere but the presence of ulcer could not be proved at the time of examination. Such ulcers, in all probability, are the result of thromboses in small gastric or duodenal vessels.

Reports of verified Curling ulcers are not too frequent. Whigham [155] reports one such ulcer in a young woman who suffered severe extensive cutaneous burns. An autopsy performed eleven days after the accident revealed a large acute ulcer in the first portion of the duodenum. There was nothing in the past history to suggest a previous ulceration. In this regard it is of some interest to mention the observations made on patients who were badly burned in the Cocoanut Grove fire in Boston.[156]. Among those patients admitted to the Massachusetts General Hospital no symptoms of ulcer were noted, but over half of the patients had occult blood in the stools. Autopsy in 3 cases showed extensive submucosal hemorrhage in the duodenum in 1 instance and duodenal and gastric lesions of a petechial nature in the other 2.

Traumatic gastroduodenal ulcers are rare but probably occur. Verdan [157] is responsible for the statement that in only 1 of 4 cases is ulcer recognized as such during life. This frequent, though unrecognized, occurrence, together with the high frequency of accidents in these days, introduces a considerable possibility of error in any conclusion as regards traumatic ulcer. Although the traumatic origin of this disease has never been clearly demonstrated, it is nevertheless possible to regard trauma as a determining cause of a chronic gastric lesion if no dyspeptic symptoms existed prior to the accident, provided that the trauma was of sufficient violence, involved the epigastrium and was followed by immediate objective symptoms. Case histories illustrate the possible etiologic importance for chronic gastric lesions of cerebral trauma, cutaneous burns, septicemia and lead poisoning. The discussion is of interest chiefly from a medicolegal point of view. Traumatic perforation of a gastric ulcer is obviously less difficult to understand than the conditions just alluded to, but such a finding is still not too common. Gallo and Pozzo [158] report traumatic perforation of a gastric ulcer following a kick in the epigastrium by a horse. A dense, firm ulcer was discovered at operation, although no history of preexisting symptoms of ulcer could be elicited. The literature is reviewed and several cases abstracted.

A fascinating study by Horton [159] concerns the production of acute duodenal ulcer in cases of cephalgia due to histamine. This condition, which has only recently been recognized, invariably presents the story of acute attacks of excruciating pain involving the eye, temple and neck and often the face. These attacks have been refractory to other types of treatment but have been eradicated within two to three weeks by "desensitization" to histamine. Ten such cases are presented by the author, in which there was a direct relationship between an acute

154. Tinney, W. S.; Hall, B. E., and Giffin, H. Z.: Polycythemia Vera and Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **18**:24, 1943.

155. Whigham, J. R. M.: Severe Burns Associated with Duodenal Ulceration, Brit. J. Surg. **30**:178, 1942.

156. Mallory, T. B., and Brickley, W. J.: Management of the Cocoanut Grove Burns at the Massachusetts Hospital: Pathology, with Special Reference to the Pulmonary Lesions, Ann. Surg. **117**:865 (June) 1943.

157. Verdan, C.: Gastro-Duodenal Ulcers as a Result of Accidents, Gastroenterologia **67**:1, 1942.

158. Gallo, A. G., and Pozzo, J. J.: Traumatic Perforation of a Gastric Ulcer, Semana méd. **2**:133, 1942.

159. Horton, B. T.: Histaminic Cephalgia Resulting in Production of Acute Duodenal Ulcer, J. A. M. A. **122**:59 (May 1) 1943.

duodenal ulcer with a crater and histamine cephalgia. The formation of the ulcer in each instance was secondary to the attacks of intractable headache. During the attacks the gastric acid rose to an abnormally high level, just as would have been the case if the patient had received approximately 0.35 mg. of histamine subcutaneously. The subjects were all hypersensitive to histamine, to such a degree that even 0.01 mg. of histamine had been sufficient in many instances to precipitate a rise in gastric acidity. Treatment by means of desensitization to histamine, without other treatment for the duodenal ulcer itself, not only caused cessation of the headaches but permitted the duodenal ulcer to heal properly, within two weeks.

Synchronous studies of gastroduodenal motility with tandem balloons have been made by Patterson and Sandweiss,[160] with particular reference to the relationship between gastroduodenal motility and symptoms associated with duodenal ulcer in the human. Distress from ulcer occurred only when the stomach and duodenum were simultaneously exhibiting motility or when the duodenum alone was showing motor activity. It did not occur when the duodenum was in a quiescent phase. In other words, the studies indicate that the duodenum must be in an active motor phase for the patient with duodenal ulcer to experience pain. As the authors point out, however, these findings do not necessarily indicate that duodenal motility is the only factor responsible for the distress associated with ulcer. In keeping with other investigative reports, these authors found that the duodenum sometimes has its periods of motor activity long before the stomach does, which indicates that the duodenum acts independently of the stomach.

A curious picture of pain like that of duodenal ulcer without the existence of an ulcer is reported by Yenikomshian and Shehadi.[161] Gastrointestinal disturbances caused by hookworm disease may appear in different clinical forms, including that of duodenal ulcer. Estimation of free gastric acid shows a rise to a level higher than that obtained in the average case of duodenal ulcer, in spite of varying degrees of severe anemia. Roentgenologic studies in these cases of ancylostomiasis show evidence of swelling of the duodenal mucosa, inconstant deformity of the duodenal bulb, hyperperistalsis of the stomach and duodenum, and usually reversed peristalsis of the duodenum without obstruction. Administration of a vermifuge results in the elimination of epigastric pain within twenty-four hours and restoration of the contour of the duodenal wall in from eleven to twenty-four days.

Articles on perforated ulcer are numerous. Of these, only a few have been taken for review. One by Harrison and Cooper [162] presents a detailed analysis of 57 cases of acute perforated peptic ulcer. The study was undertaken in order to test the validity of the widespread opinion that if a peptic ulcer perforates and the patient recovers after closure, subsequent permanent healing of the ulcer is to be expected. Of 41 patients surviving perforation, less than one fifth remained well; 25 had an asymptomatic period immediately following operation, averaging one and eight-tenths years; 7 patients had continuous symptoms. The patient reporting the longest asymptomatic period had this period abruptly terminated by a second perforation. The authors conclude that after closure of a perforated

160. Patterson, T. L., and Sandweiss, D. J.: The Relationship Between Gastro-Duodenal Motility Phases and Symptoms Associated with Duodenal Ulcer in the Human, Am. J. Digest. Dis. **9**:375, 1942.

161. Yenikomshian, H. A., and Shehadi, W. H.: Duodenal Ulcer Syndrome Caused by Ankylostomiasis: Report of Twenty-Five Cases with Gastric Acidity and Roentgenologic Studies, Am. J. Roentgenol. **49**:39, 1943.

162. Harrison, C., and Cooper, F. W., Jr.: Immediate and Late Results of Perforation of Peptic Ulcer, Ann. Surg. **116**:194, 1942.

ulcer every patient should have his case evaluated anew and be treated as any other patient with ulcer. A slightly more optimistic report is that of Barber and Madden,[163] who carried out a follow-up study on a small group of 21 patients with perforated ulcers. Two thirds of these were considered to be free of symptoms of ulcer but such a finding is not in accord with the usual clinical experience.

Activity of peptic ulcer during pregnancy is rare, and complications are still more uncommon. For this reason, the discussion by Sandweiss and his collaborators [164] on deaths from perforation of gastroduodenal ulcer during pregnancy and puerperium is of interest. One such case is reported, and the literature is completely reviewed. In all, 14 cases have been reported, and the point is made that for pregnant women who have a previous history suggestive of ulcer medical management should be immediately instituted if epigastric symptoms occur during the second or third trimester of pregnancy. Another rare complication is that reported by Heathfield [165] who records the death of a patient from a solitary abscess of the liver secondary to a perforated duodenal ulcer.

Ulfelder and Allen [166] have made an analysis of 334 cases of patients with acute perforation of a gastric or duodenal ulcer, seen between 1916 and 1940. The mortality by five year periods showed no significant change during the past fifteen years. During the winter months the mortality was appreciably higher than during other seasons, and there appeared to be some relation between this mortality and the virulence of recurrent infections of the respiratory tract. As was to have been expected, the mortality rose with the patient's age. In agreement with all experienced surgeons, they noted that the interval between perforation and closure is of fundamental prognostic importance. An interesting fact is the observation that in the majority of patients who recovered when more than fifteen hours had elapsed between the onset and operation, the perforation had already spontaneously healed.

Sanders [167] reports an unusual combination of perforated peptic ulcer and acute appendicitis. Nine other such cases have been reported. The preoperative diagnosis in all the cases reviewed was acute appendicitis, with or without perforation, and only postoperatively was the existence of the two lesions found. The wisdom of the long-established rule to operate whenever the diagnosis of appendicitis is made is reaffirmed.

Allusion has already been made to a possible new procedure in surgical treatment for ulcer—namely, insertion of jejunal transplants in the gastric wall. Andrus, Lord and Stefko [168] have shown in animals that gastroenterostomy alone failed to prevent a marked diminution in the average p_H of the mucosa of seven

163. Barber, R. F., and Madden, J. L.: Acute Gastroduodenal Perforation, Am. J. Surg. **59**:484, 1943.

164. Sandweiss, D. J.; Podolsky, H. M.; Saltzstein, H. C., and Farbman, A. A.: Deaths from Perforation and Hemorrhage of Gastroduodenal Ulcer During Pregnancy and Puerperium: A Review of the Literature and Report of One Case, Am. J. Obst. & Gynec. **45**:131, 1943.

165. Heathfield, K. W. G.: Liver Abscess Following Perforated Duodenal Ulcer, Lancet **2**:155, 1942.

166. Ulfelder, H., and Allen, A. W.: Acute Perforation of Ulcers of the Stomach and Duodenum, New England J. Med. **227**:780, 1942.

167. Sanders, A. W.: Perforated Peptic Ulcer Complicated by Acute Purulent Appendicitis: Case Report, Am. J. Surg. **57**:364, 1942.

168. Andrus, W. deW.; Lord, J. W., Jr., and Stefko, P.: Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the p_H of the Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**:99, 1943. Lord, J. W., Jr.; Andrus, W. deW., and Stefko, P.: Effects of Jejunal Transplants on the Experimental Production of Peptic Ulcers, Arch. Surg. **46**:459 (April) 1943.

different regions of the stomach following injection of histamine. After conversion of the gastroenterostomy to a jejunal graft, however, the normal response to histamine was reversed in all 6 dogs. After these experiments the effects of such jejunal transplants were studied on the experimental production of peptic ulcers of the duodenum through daily intramuscular injection of a mixture of histamine phosphate and beeswax in liquid petrolatum, as reported by Varco and his associates (1941). In the single animal in which it could be satisfactorily carried out, implantation of a pedicle graft of jejunum into the stomach was followed by healing of the duodenal lesions despite continuation of the injections of histamine. The results also suggest the efficacy of such transplants in preventing the development of duodenal erosion and ulceration during continued exposure to histamine.

The adequacy of most statistical methods for evaluating the results in the treatment for peptic ulcer is severely criticized by Hollander and Mage.[169] These authors give an excellent discussion of this phase of the problem of ulcer and present a statistical procedure of their own which appears to be satisfactory. On the basis of such statistical studies, they analyze the surgical results in patients with duodenal ulcer who were subjected to subtotal gastrectomy during the years 1923 to 1934. In this group, the average total incidence of recurrence was about 9 per cent, a much higher figure than that which is usually considered. A careful perusal of the points made by these authors is recommended to those who are interested in carrying out statistical studies. Mage[170] subsequently carried out a statistical analysis of the cases of 600 patients with ulcer on whom subtotal gastrectomies had been performed in the last seventeen years. In 502 patients with duodenal ulcer and 98 with gastric ulcer thus treated, there were 41 recurrences (all but 1 taking place in patients with duodenal ulcer), or approximately a 7 per cent incidence of recurrence. Recurrence of ulcer was not noted before the expiration of a year postoperatively, and in the majority of cases it was found in the first four years following operation. One recurrence, however, was recorded after twelve years of freedom from symptoms. Of the entire group of resected specimens, 30 contained the ulcer; hence removal of the ulcer at operation is not a sine qua non for insuring success of subtotal gastrectomy. No ulcers occurred in patients without free hydrochloric acid in the gastric secretion. Subtotal resection created achlorhydria in at least 90 per cent of patients with gastric ulcer and in about 50 per cent of those with duodenal ulcer. A final conclusion, with which the reviewer is in entire sympathy, is that: "Radical resection is considered to be the best available operation for duodenal ulcer, but the present impression is that it leaves much to be desired."

The mortality subsequent to subtotal gastric resection for ulcer is relatively low. Miller[171] gives a mortality of 2.8 per cent in his entire group of 230 cases in which the operation was done. This group comprised instances of all types of ulcer, including those complicated by gross and massive hemorrhage. Lahey and Marshall[172] cite a similar mortality of 2.7 per cent for all gastric, duodenal, and gastrojejunal ulcers, exclusive of gastrojejunocolic fistulas. A mortality of 3.2 per cent is reported by them for 251 subtotal resections for ulcers of all types,

169. Hollander, F., and Mage, S.: A Statistical Method for Evaluating the Results of Treatment for Peptic Ulcer, Surg., Gynec. & Obst. **76**:533, 1943.

170. Mage, S.: Recurrence of Ulceration Following Subtotal Gastrectomy in the Treatment of Gastroduodenal Ulcer, Ann. Surg. **116**:729, 1942.

171. Miller, G. G.: Report of Two Hundred and Thirty Cases of Subtotal Gastric Resection for Peptic Ulcer, Surgery **12**:383, 1942.

172. Lahey, F. H., and Marshall, S. F.: Surgical Management of Some of the More Complicated Problems of Peptic Ulcer, Surg., Gynec. & Obst. **76**:641, 1943.

and a 4.4 per cent rate for 46 consecutive subtotal resections performed solely for gastrojejunal ulcers. These authors rightly stress the wisdom of such radical surgical treatment as the only successful means of handling the particular problem of gastrojejunal ulcer. Experience seems to be unanimous that medical measures are not effective in preventing chronic invalidism for patients with this condition. Delgado [173] cites an even lower mortality following gastrectomies on more than 500 patients with ulcer. This author claims that only 2 per cent of patients failed to survive the operation, and he mentions only 1 recurrent ulcer. In view of Hollander's remarks on a collection of statistics of late surgical results, it is pertinent to point out that of a group of 500 patients only 75 were followed; therefore, the statistical value of this particular communication is invalidated.

Subtotal gastrectomy is far from a physiologic procedure, and it is true that many patients subjected to this form of operation are far from free of symptoms, in spite of the fact that specific symptoms of ulcer may be lacking. Freeman and his collaborators [174] attempted a detailed study to determine the effect of complete removal of the stomach from growing monkeys. Five of the 6 gastrectomized animals died within one hundred and twenty-eight to one hundred and fifty-two days following gastrectomy. Death was always preceded by anorexia, lassitude, diarrhea and dehydration, and in 1 instance there was presence of gross blood in the stools. One animal survived for a year and a half but failed to gain weight. The animal that lived the longest differed from its control as follows: The emptying time of the upper part of the small intestine was increased; the animal failed to gain weight; the serum phosphatase was increased; the serum calcium was decreased; the parathyroid gland was enlarged and contained large cells with vacuolated cytoplasm; the stools were intermittently watery and foul smelling; there was a diminution in the size of the skeleton.

Evensen [175] studied alimentary hypoglycemia in 38 patients who had been subjected to gastroenterostomies and in 95 who had had subtotal gastrectomies. Of 100 control subjects, 7 per cent described hypoglycemic symptoms during dextrose tolerance tests. Thirty per cent of those patients with gastroenterostomies had similar symptoms after dextrose tolerance tests, and 15 per cent of the group of patients on whom subtotal gastrectomies had been performed. Evenson's investigations also revealed that the performance of any work after meals may be a contributing factor to the production of hypoglycemic symptoms in patients after operations on the stomach.

The effect of subtotal gastric resection on gastric acidity was studied by Friedell, Shaar and Walters.[176] These authors obtained a reduction of gastric acidity in 75 per cent of the cases of duodenal ulcer for which this operation was performed and a relative achlorhydria in all of the cases of gastric ulcer. Histamine stimulation in many of the relatively achlorhydric patients still produces secretion of free acid. The optimal amount of stomach to be removed would seem to be somewhere between one half and two thirds, according to Holman and McSwain.[177] Their

173. Delgado, R.: The Life of the Gastrectomy Patient: Results of Gastrectomy for Gastric and Duodenal Ulcer, Arch. argent. de enferm. d. ap. digest. y de la nutrición **17**:590, 1942.

174. Freeman, S.; Hough, V. H.; Wigodsky, H., and Ivy, A. C.: The Effect of Gastrectomy upon Growing Monkeys, Gastroenterology **1**:199, 1943.

175. Evensen, O. K.: Acta med. Scandinav., 1942, supp. 126; cited in Alimentary Hypoglycaemia After Stomach Operations, editorial, Lancet **2**:626, 1942.

176. Friedell, M. T.; Shaar, C. M., and Walters, W.: Effect of Gastric Resection on Gastric Acidity, J. A. M. A. **120**:666 (Oct. 31) 1942.

177. Holman, C. W., and McSwain, B.: Gastric Acidity Following Gastric Resection, Surgery **13**:916, 1943.

postoperative results seem to indicate that removal of more than two thirds of the stomach does not increase to any important degree the number of patients with reduced acidity or anacidity.

In an attempt to evaluate surgical procedures Hinton [178] discusses the intractable duodenal ulcer and expresses the opinion that the only true indication of intractability in cases of duodenal ulcer is constant pain. He does not agree that pyloric stenosis as such is an indication for surgical intervention, and he feels that a stenosing or obstructing ulcer not accompanied by pain does not require surgical intervention. Such a statement seems overconservative and to require a definition of the term stenosis. It is not infrequent to have a degree of pyloric stenosis sufficient to interfere with normal nutrition and still have no symptoms of active ulcer. In these cases, it certainly would seem the part of wisdom to relieve the situation by an adequate surgical procedure. Another statement that seems to require comment is that patients who will not cooperate under medical management should not be operated on. Such an attitude hardly seems justifiable, inasmuch as there are many instances in which complete and adequate cooperation is impossible because of economic or social reasons, and in many of these cases an adequate surgical operation again is effective although at times the results are much less satisfactory than in patients who fully understand their condition and the requirements of medical treatment. In a report by Collins and Ward [179] overconservatism against reasonable surgical intervention again seems to be apparent. These authors review their experience with 29 jejunal ulcers, all postoperative. They conclude that for the uncomplicated postoperative jejunal ulcer adequate medical treatment persistently carried out until healing is assured, with careful control of the patient's regimen for an indefinite period afterward, constitutes the safest plan of treatment. This does not coincide with the conviction of most doctors who are conversant with the problem of ulcer. In most persons with postoperative jejunal ulcer recurrences are frequent and complications not uncommon. Modern gastric operations when performed by adequately trained surgeons can be done with a minimum of risk and a maximum of postoperative health for this distressing postoperative complication. Even under the best conditions of medical regimen, few patients suffering from this type of ulcer fail to have recurrences.

One of the complications of gastroenterostomy is reported by Smith and Rivers,[180] namely, gastroileal ulcer. These authors report 9 cases of gastroileostomy, an important but fortunately rare surgical error. Gastroileitis was present in 1 of these cases and gastroileal ulcer in 3. The symptoms, as should be expected, were entirely similar to those of gastrojejunal ulcer.

The occasional indication for jejunal alimentation in the surgical management of peptic ulcer is discussed by Colp and Druckerman.[181] Jejunostomy for alimentation was performed in a series of 51 patients suffering from recurrent peptic ulcer. It was used as a preliminary, palliative, complementary and supplementary measure in the surgical treatment of peptic ulcer. The indications for and clinical applications of this maneuver are fully described. Such a procedure

178. Hinton, J. W.: The Intractable Duodenal Ulcer: Evaluation of Surgical Procedures, Ann. Surg. **117**:498, 1943.

179. Collins, E. N., and Ward, G. J.: Current Trends in the Treatment of Jejunal Ulcer, Cleveland Clin. Quart. **9**:159, 1942.

180. Smith, L. A., and Rivers, A. B.: Gastroileostomy and Gastroileal Ulcer, Surg., Gynec. & Obst. **76**:110, 1943.

181. Colp, R., and Druckerman, L. J.: The Indications for Jejunal Alimentation in the Surgery of Peptic Ulcer, Ann. Surg. **117**:387, 1943.

is not commonly used but for badly depleted patients may offer an effective way of shortening convalescence and of avoiding serious postoperation depletion.

Although not limited to the results of surgical treatment of ulcer, the problem of intestinal distention complicating abdominal operation is an important one. In a large percentage of cases, gaseous distention of the intestine is due to swallowed air. Proof of this is mentioned in an article by Singleton, Rogers and Houston,[182] who note that patients with excision of the esophagus or with a complete stricture and gastrostomy feeding rarely have appreciable amounts of gas in the bowel. The measures that are needed to combat postoperative distention, which is undoubtedly aggravated by the effects of anesthesia and preoperative and postoperative medication with morphine, are fairly well accepted, but these authors review in detail the various measures that are indicated and provide an adequate guide for their rational use. A complete discussion of the advantages and disadvantages of gastric suction before and after operation is also to be found in this article. Gastric retention postoperatively frequently has been attributed to the edema associated with hypoproteinemia. That such edema may play an important role when localized in an anastomotic stoma is indisputable. For this reason the attempt by Chauncey and Gray [183] to estimate the actual role played by the concentration of the serum proteins in the production of gastric retention is of interest. These authors studied groups of postoperative patients in whom distention was present or failed to occur after operation was performed on the upper portion of the gastrointestinal tract. They found that the fluctuation in amount of gastric retention was not paralleled in any way by fluctuations in the concentration of serum protein or of the albumin fraction or in the colloidal osmotic pressure of the serum. The retention frequently diminished and disappeared with a coincidental decrease in the osmotic pressure and in the concentration of protein. The presence of clinical edema caused by hypoproteinemia was noticed postoperatively at the same time gastric retention finally disappeared. Such findings would tend to throw doubt on the importance of the role played by hypoproteinemia in postoperative gastric retention. Unfortunately, a proper estimate of other variables conducive to the formation of edema in an operative stroma were not available. These variables would include the degree of activity of the ulcerative process at the time of operation and the actual administration of water and electrolytes in relation to the presence of variations in serum protein.

A realization on the part of surgeons that more rapid mobilization of patients operated on for diseases of the digestive tract may be a proper therapeutic procedure is evidenced in the articles by Joseph [184] and González-Bueno.[185] In a discussion of the treatment of acute dilatation of the stomach following operative procedures, Joseph observed that all patients in whom this condition developed had only one common factor—namely, enforced confinement to bed following the operative procedure. In the presence of acute postoperative gastric dilatation, he has in recent years proceeded to stand the patient upright and aid him in taking a few steps, in spite of obvious postoperative weakness and depletion. The treatment apparently was successful in correcting the condition. González-Bueno [185] goes so

182. Singleton, A. O.; Rogers, F., and Houston, F. G.: The Problem of Intestinal Gases Complicating Abdominal Surgery, Ann. Surg. **115**:921, 1942.

183. Chauncey, L. R., and Gray, H. K.: The Relationship of the Concentration of Proteins in the Serum to Postoperative Gastric Retention, Gastroenterology **1**:72, 1943.

184. Joseph, E. G.: A New Treatment for Acute Dilatation of the Stomach, Am. J. Surg. **60**:381, 1943.

185. González-Bueno, C.: Immediate Mobilization of Those Operated on for Disease Conditions of Digestive Tract: Results in Seventy-Four Cases, Rev. clín. españ. **6**:405, 1942.

far as to insist that patients should leave the operating table on their own feet. He reviews 74 consecutive laparotomies in which the postoperative treatment was ambulatory, the operations being on the stomach, the biliary tract, the liver or the intestine. Newburger [186] contributes a similar point of view in a study of the influence of exercise on wound healing in rats. Standardized laparotomy wounds were produced in rats at intervals of three, five and ten days. The strength of the wounds was determined in animals which were kept at rest and in others which were exercised. Exercise rather than immobilization was found to hasten the increase in tensile strength of the experimental abdominal incision. Such a conception of postoperative care is worthy of serious thought, even if modifications and exceptions are needed. There can be little doubt that prolonged and absolute immobilization is the ideal procedure for the production of many postoperative complications.

The preceding comments have had chiefly to do with the surgical approach to the problem of ulcer. It is still true that the vast majority of patients with ulcer should be managed by medical procedures, but there is little that is novel or untried in the current literature. Various reports on antacid therapy by the use of alkalis, colloidal aluminum hydroxide and various drip methods are to be found but deserve little more than passing comment. Rossett and Flexner,[187] after continuous recordings of the gastric p_H in situ, conclude that milk or aluminum hydroxide in adequate dosage best fulfils the physiologic criteria of an ideal antacid. The efficacy of the drip method in the reduction of gastric acidity is reviewed by Cornell and his associates,[188] who claim that this method possesses advantages over the intermittent procedures by a more effective control of night pain, reduction in the time of hospitalization required for healing of the ulcer, and the possibility of administering an adequate diet with simultaneous continuous control of interdigestive gastric secretion. In difficult cases there seems little reason to doubt that the drip method, with use of milk or a colloidal gel, is extremely effective, but there is still reason to believe that it represents an unnecessary refinement in most simple cases of duodenal ulcer.

In view of possible difficulties secondary to the rationing of food, a note by Nye [189] is of passing interest. He stresses the nutritional and also the practical value of a free use of potatoes in the diet for patients with ulcer, because of their large content of minerals and of vitamins A, B_1 and C and their alkaline reaction.

The current use of amino acids, particularly for undernourished, depleted patients suffering from gastrointestinal disease, has led to a study of the effect of the oral administration of a solution of a mixture of amino acids on gastric acidity by Levy and Siler.[190] These authors show that an orally administered mixture of amino acids is an effective buffering agent when introduced into the stomach. Free acid is consistently reduced, and peptic activity is reduced to a minimum. The mixture can be given safely to normal persons without the mildest discomfort, and in the treatment of ulcer, even in the presence of bleeding, its use seems justified.

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186. Newburger, B.: Early Postoperative Walking: I. The Influence of Exercise on Wound Healing in Rats, Surgery **13**:692, 1943.

187. Rossett, N. E., and Flexner, J.: A Method for the Continuous Recording of Gastric p_H in Situ: IV. Further Evaluation of the Efficacy of Antacids in Vitro and in the Human Being, Ann. Int. Med. **18**:193, 1943.

188. Cornell, A.; Hollander, F., and Winkelstein, A.: The Efficacy of the Drip Method in the Reduction of Gastric Acidity, Am. J. Digest. Dis. **9**:332, 1942.

189. Nye, L. J. J.: Potato Diet in Peptic Ulcer, M. J. Australia **1**:7, 1943.

190. Levy, J. S., and Siler, K. A.: Clinical Studies of Amino Acids: I. The Effect of Oral Administration of a Solution of an Amino Acids Mixture on Gastric Acidity, Am. J. Digest. Dis. **9**:354, 1942.

Kirsner and Palmer [191] continued their studies on the alkalosis developing during "Sippy" treatment. The results in a large number of patients with ulcer indicate that alkalosis complicating Sippy treatment with calcium carbonate can be prevented in almost all instances by the concurrent administration of adequate amounts of sodium chloride. The therapeutic action of sodium chloride they attribute largely to the increased excretion of base bicarbonate in the urine, at the expense of the bicarbonate in the blood, after the administration of salt. In occasional cases sodium chloride therapy was apparently not only inadequate to forestall the development of alkalosis but insufficient to correct the acid-base disturbance. They believe it possible that in these few cases insufficient amounts of salt were given and the excretion of the amount of bicarbonate in the urine was retarded by antecedent impairment of renal function. In a separate article [192] they record an unusual incidence of extreme tolerance to massive quantities of sodium bicarbonate. Their case was that of a patient with ulcer who had been twice hospitalized because of massive hemorrhage. Studies of renal function gave normal results, and the administration of 32,000 Gm. of sodium bicarbonate in twenty months produced no marked alteration in the acid-base balance and no decrease in the urea clearance.

Warren, Front, and Kirsner [193] studied the effect of antacid therapy on the peptic activity of gastric juice in a group of persons, including several patients with ulcer. Their results indicated that the inhibition of peptic activity in man appears to be related to the increase in p_H of the gastric juice toward neutrality but that for a given p_H aluminum hydroxide apparently exerts a greater antipeptic effect than calcium carbonate. The treatment of peptic ulcer with milk and cream, in frequent small feedings, and either calcium carbonate or aluminum hydroxide reduces the peptic activity of human gastric contents.

Confirmation of the results previously reported by Palmer and his associates on the effect of irradiation of gastric acidity is to be found in an article by Jenkins and McGeorge.[194] A heavy dose of intragastric radiation was produced by the use of radium needles secured at the end of a stout rubber tube and swallowed by the patient. Reduction in the acidity and volume of the gastric juices following irradiation was demonstrated in 13 of the 14 patients with ulcer treated, and clinical improvement accompanied chemical changes in the gastric juice. Such a procedure would seem to be unnecessarily clumsy by comparison with the deep roentgen therapy practiced by Palmer, and the results were no better. These authors, like Palmer, found that gastric acidity does not remain at a low level indefinitely after irradiation but that it gradually tends to rise again toward normal.

The effect of endocrine therapy in gastroduodenal ulceration has been investigated in human beings by Abrahamson, Church and Hinton.[195] These authors point out that males and females have an approximately equal number of peptic

191. Kirsner, J. B., and Palmer, W. L.: Value of Sodium Chloride in Prevention of Alkalosis During "Sippy" Treatment with Calcium Carbonate, Arch. Int. Med. **71**: 415 (March) 1943.

192. Kirsner, J. B., and Palmer, W. L.: Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function: Report of a Case with Remarkable Tolerance, Ann. Int. Med. **18**:100, 1943.

193. Warren, I. A.; Front, J., and Kirsner, J. B.: The Effect of Antacid Therapy on the Peptic Activity of Gastric Juice in Man, Gastroenterology **1**:102, 1943.

194. Jenkins, J. A., and McGeorge, M.: Control of Radium for Gastric Acidity, Arch. Int. Med. **70**:714 (Nov.) 1942.

195. Abrahamson, R. H.; Church, R., and Hinton, J. W.: Hormone Effects on the Male Gastroduodenal Mucosa, Am. J. M. Sc. **204**:809, 1942. Abrahamson, R. H., and Hinton, J. W.: The Gastric Mucosa as an Endocrine Gland, Surg., Gynec. & Obst. **76**:147, 1943.

ulcers before puberty when their hormonal balance is as yet not well established. Following puberty and synchronously with the change in the androgen-estrogen ratio, the peptic ulcer ratio changes to 9 males per 1 female. Peptic ulcer occurs frequenlty in females during and immediately following the menopause. Because of these facts, a group of male patients with duodenal ulcer who previously had responded unsuccessfully to other forms of therapy for ulcer for a year or longer were placed on daily injections of varying doses of estrogen substance (estrone in oil). The results of this treatment appeared to be favorable in that there was a higher percentage of remissions than is usual in controls (82 per cent). Of greater importance is the fact that healing of the duodenal lesion occurred in nearly half of the subjects, in spite of a definitely increased free and total acidity, a point which casts some doubt on the view concerning the relationship between the healing of a duodenal ulcer and measures directed toward lowering gastric acidity. These same investigators also observed the effect of thyroid and thyroxin medication in a group of patients with ulcer. No conclusive results were obtained.

Miscellaneous Gastric Conditions.—Miscellaneous and odd gastric lesions are worthy of short comment. A report by Browne and McHardy [196] on the pseudo-cascade stomach is of importance largely in differentiating this condition from the "hourglass" stomach, with which it is frequently confused in the American literature. In a cascade stomach the upper portion of the stomach is a flaccid, posteriorly flopped sac devoid of peristalsis; the lower, and main, portion of the stomach is a normal peristaltic organ. Characteristically the upper portion fills, and the contents cascade over into the lower portion with changes in position, especially when the patient lies on the left side. A transitory type may occur occasionally, due to spasm of the oblique muscle of the stomach, to an organic defect caused by a gas-filled splenic colon displacing an abnormally fixed or ptosed stomach or to a benign or malignant intragastric deformity. The diagnosis is roentgenologic. In the case reported by these authors the cardiac portion of the stomach was markedly distorted and cascading was produced by distention of the splenic flexure with air. A mild superficial gastritis in the cardiac loculus was present. Laparotomy showed adhesions along the lesser curvature and part of the anterior gastric wall, producing a short gastrohepatic ligament and fixation. Section of the adhesions permitted a good recovery and freedom from symptoms a year later. A somewhat similar example of cascade stomach is reported by Charbonnier,[197] in which biloculation of the stomach was caused by the transverse colon pressing against it from behind. At operation, a thick, fibrous band, running from the region of the abdominal wall near the spleen toward the splenic flexure and constricting the descending colon immediately below the flexure, was found. Division of the adhesions immediately reestablished normal gastric and colonic relationships.

Gastric diverticulum is uncommon, although it has been known since 1774. Sixty-five per cent of the diverticula occur in the greater curvature at the cardiac end of the stomach, according to Love,[198] who reports such an anomaly. A detailed study of 35 cases of gastric diverticulum is presented by Tracy.[199] One case in particular is of interest, in which a prepyloric diverticulum caused recurrent gastric obstruction.

196. Browne, D. C., and McHardy, G.: Pseudo-Cascade Stomach: Case Report, Am. J. Digest. Dis. **10**:224, 1943.

197. Charbonnier, A.: A Case of Mid-Gastric Occlusion Caused by a Transverse Megacolon of Mechanical Origin, Gastroenterologia **67**:55, 1942.

198. Love, McN.: Gastric Diverticulum, Brit. J. Surg. **30**:180, 1942.

199. Tracey, M. L.: Gastric Diverticula, Gastroenterology **1**:518, 1943.

Prolapsed gastric mucosa causing symptoms of pyloric obstruction has been recognized by roentgenologists for some years. Diagnoses are not common, however, and accordingly the report of 4 cases by Melamed and Hiller [200] is of interest. In 1 instance severe melena arising from 2 ulcers on the prolapsing mucosa was the first outstanding symptom. One of these ulcers was demonstrated roentgenologically.

Interesting case reports of tuberculosis of the stomach and syphilis of the stomach, respectively, are recorded by Hartz and van der Sar [201] and by Palmer and his associates.[202] Roentgen studies on 225 patients with pellagra are reported by Díaz-Rubio and Roldán.[203] The most noteworthy feature observed by the last-mentioned authors was diminution of gastric peristalsis, which often gave rise to great dilatation and retarded evacuation of gastric contents. The mucosa was atrophic in over two thirds of the cases, but in about one fourth the roentgenologic appearance of the stomach was normal as regards tonus, peristalsis, evacuation and mucosal relief, in spite of the fact that pellagra was fully developed. There were some cases in which no relationship existed between the severity of the changes and the gravity of the clinical picture, but in 59 patients, on whom at least three studies were made, there was a close parallelism between the clinical picture and the intensity of the roentgenologic signs.

Autopsy studies on the stomachs of patients dying from pernicious anemia were made by Cox.[204] In 2 instances the patients had had continuous successful liver therapy for ten and thirteen years, respectively, and there was no anemia at the time of death. Results of the examinations showed that almost complete replacement of the normal mucosal glands, of the fundic type, by abnormal, less differentiated glands had taken place. The pyloric zone was only slightly altered. No relationship could be found between the appearance of the stomach and the duration of the disease or of the treatment. The stomach from a well studied case of long-standing sprue with fatal macrocytic anemia showed no comparable change. The authors suggest that the gastric lesions in cases of pernicious anemia are different from those accompanying other diseases and may represent a specific change, possibly the result of massive destruction of the highly differentiated parietal and chief cells. Such histologic observations are of interest inasmuch as they indicate that the gross regeneration of the gastric mucosa, which can be readily demonstrated by gastroscopy following successful therapy of pernicious anemia, must represent a replacement of the highly differentiated mucosal cells by others that are functionally different. The difference between these changes in pernicious anemia and those occurring in sprue are commented on in detail by Olleros.[205] Like patients with pernicious anemia, the vast majority of patients with tropical sprue show invasion of the stomach by the gram-negative flora of the large intestine. The mucosal atrophy observed in the gastroscopic examination of patients with sprue is less marked than that occurring in pernicious anemia in temperate climates. Patients with tropical sprue eliminate neutral red by the

200. Melamed, A., and Hiller, R. I.: Prolapsed Gastric Mucosa: Roentgenologic Demonstration of Ulcer Crater in Prolapsed Polypoid Mucosa, Am. J. Digest. Dis. **10**:93, 1943.

201. Hartz, P. H., and van der Sar, A.: Ulcerative Tuberculosis of the Stomach, Am. Rev. Tuberc. **47**:46, 1943.

202. Palmer, W. L.; Schindler, R.; Templeton, F. E., and Humphreys, E. M.: Syphilis of the Stomach: A Case Report, Ann. Int. Med. **18**:393, 1943.

203. Díaz-Rubio, M., and Lara Roldán, L.: Casal's Disease: Roentgen Behavior of Stomach in Pellagra, Rev. clín. españ. **4**:408, 1942.

204. Cox, A. J.: The Stomach in Pernicious Anemia, Am. J. Path. **19**:491, 1943.

205. Rodriguez Olleros, A.: Gastric Similarities and Differences Between Tropical Sprue and Pernicious Anemia, Am. J. Digest. Dis. **9**:261, 1942.

gastric mucosa, even when there exists a histamine-resistant achylia. This is suggested by the author as a means of differentiating between tropical sprue and pernicious anemia.

Cancer of the Stomach.—The difficulty in obtaining early diagnoses of gastric cancer is a perennial one. Too frequently the diagnosis is not made early because of carelessness and an inadequate history. Some of the difficulties in the roentgenologic diagnosis of gastric cancer are outlined by Kirklin,[206] who presents a thorough discussion of the entire subject of roentgenologic diagnosis of gastric cancer. He correctly points out that roentgen examination will exhibit any gastric lesion that is capable of producing symptoms or that can be seen macroscopically, and failure to discern it should be charged to the examiner, not to the method. Cancer of the cardia is particularly likely to be missed unless the region of the gas bubble is inspected closely. More common are the failures or mistakes in differential diagnosis of cancer from benign lesions. Kirklin states that most misunderstandings could be avoided if to the roentgenologic diagnosis of benign tumor were added the caution that such tumors are partly malignant, and to the diagnosis of gastric ulcer the reminder that about one tenth of such ulcers, even though they appear roentgenologically benign, are cancerous.

The gastroscopic diagnosis of gastric cancer, although a tremendous additional help, is also subject to serious error. Schiff [207] discusses gastroscopic examinations in 78 cases of proved gastric cancer. In 53 cases the lesion was seen and correctly diagnosed, and in 7 gastroscopic examination was the sole means of revealing the presence of the tumor. In 17 instances technical difficulties prevented visualization of the lesion, and in 9 it was mistaken for a benign gastric ulcer. Similar difficulties are reported by Freedman and his associates,[208] who record 5 cases in which the roentgenologic and gastroscopic appearance of localized chronic hypertrophic gastritis simulated carcinoma of the stomach. Moersch and Weir [209] cite an unusual difficulty confronting the gastroscopist, namely, differentiation between prolapsed mucosa and gastric carcinoma.

The question of the causation of gastric cancer is discussed by various investigators and clinicians. Nettleship [210] points out the peculiarities of the gastric mucosa of man and compares it with that of other species. The precancerous conditions of the mucosa are then described, and special consideration is given to the concept of the possible origin of gastric cancer from a chronically damaged mucosa. The author expresses the belief that long time factors are involved in the production of human cancer and assumes that this time factor will have to be duplicated experimentally. Experimental agents must be used to stimulate those conditions of the gastric mucosa most commonly found associated with human gastric cancer, i. e. polyps, chronic gastritis and ulcer. Stout [211] focuses attention on the precancerous stomach, the gross forms assumed by early carcinoma, its method of spread and its differentiation from other kinds of gastric lesions. On the basis of an examination of over 400 specimens, he states that it is entirely

206. Kirklin, B. R.: Mistakes and Misunderstandings in the Roentgenologic Diagnosis of Gastric Cancer, Arch. Surg. **46**:861 (June) 1943.

207. Schiff, L.: Gastroscopic Diagnosis of Gastric Cancer, Arch. Surg. **46**:865 (June) 1943.

208. Freedman, E.; Glenn, P. M., and Laipply, T. C.: Chronic Gastritis Simulating Gastric Carcinoma: Report of Five Cases, Arch. Int. Med. **71**:23 (Jan.) 1943.

209. Moersch, H. J., and Weir, J. F.: Redundant Gastric Mucosa Simulating Carcinoma of the Stomach, Am. J. Digest. Dis. **9**:287, 1942.

210. Nettleship, A.: Experimental Gastric Carcinoma, Arch. Surg. **46**:793 (June) 1943.

211. Stout, A. P.: Pathology of Carcinoma of the Stomach, Arch. Surg. **46**:807 (June) 1943.

unknown and unproved whether or not there is a consequential relationship between so-called chronic gastritis and its glandular changes and gastric cancer. He too stresses the importance of the directional growth in different carcinomas and the need for looking for cancer in stomachs with gastritis, peptic ulcer or adenomatous polyps.

The relationship between cancer and atrophic gastritis has been stressed by Schindler and others, but, as already noted, no causative connection has been found between the two conditions. Guiss and Stewart [212] conclude, from a study made on a large number of stomachs obtained immediately or a few hours after death, that the claim that chronic atrophic gastritis is a precancerous lesion is unsupported by their observations. Atrophic changes in the stomach represent a common condition of advanced age, and both atrophy and cancer appear to be common in aging organs, but no causal relationship was found. Judd [213] also has undertaken a histologic study of the residual lesions of ulcerative gastritis, in trying to determine a possible relationship to the development of cancer. In addition to the microscopic study of 200 carcinomas of the stomach removed at operation or necropsy or both, 78 control specimens obtained from a "younger" and a "comparable" age group were examined. The frequent occurrence of certain residual lesions in carcinomatous stomachs was compared to the occurrence of such lesions in non-carcinomatous stomachs. The fundamental difference between the two is the relative lack of mucous cell hyperplasia in the latter. Essentially similar lesions occurring at a distance from a gastric carcinoma suggested to the author that the entire gastric mucosa had undergone change and that much time had been taken for this to occur. He concludes that carcinoma develops in a previously damaged stomach. An interesting observation is that reported by Jankelson and associates [214] in a study of the relationship between atrophic gastric mucosa and carcinoma of the stomach. Eighteen patients, chiefly women between the ages of 30 and 50, were carefully studied over two years, and no other pathologic change than the atrophic gastritis was found. In 2 instances a polyp developed during the period of observation. Such an occurrence is remarkable and warrants the authors' conclusion that atrophy of the gastric mucosa, with or without pernicious anemia, should be considered as a potential precancerous lesion. They believe that the development of a cancer of the stomach is probably by way of a polyp and is almost invariably preceded by achlorhydria. An additional study was made of 100 clinically proved cases of pernicious anemia, in which were found 4 proved cases of cancer of the stomach. Doehring and Eusterman [215] report 17 cases of cancer of the stomach encountered in a total of 1,014 cases of pernicious anemia, an incidence of 1.7 per cent. The development of pernicious anemia preceded the diagnosis of cancer by an average interval of almost nine years, a fact that probably accounts for the present increasing frequency of gastric cancer in association with pernicious anemia. An unusual occurrence is that reported by White [216] of simultaneous cancer and tuberculosis of the stomach in a case of pernicious anemia.

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212. Guiss, L. W., and Stewart, F. W.: Chronic Atrophic Gastritis and Cancer of the Stomach, Arch. Surg. **46**:823 (June) 1943.

213. Judd, E. S., Jr.: Residual Lesions of Ulcerative Gastritis: Possible Relationship to the Development of Carcinoma of the Stomach, Surg., Gynec. & Obst. **75**:424, 1942.

214. Jankelson, I. R.; McClure, C. W., and Freedberg, H.: Relation of Atrophic Gastric Mucosa to Carcinoma of the Stomach, Rev. Gastroenterol. **10**:26, 1943.

215. Doehring, P. C., and Eusterman, G. B.: Association of Pernicious Anemia and Carcinoma of the Stomach, Arch. Surg. **45**:554 (Oct.) 1942.

216. White, R. R.: Simultaneous Carcinoma and Tuberculosis of the Stomach in a Case of Pernicious Anemia, Proc. Staff Meet., Mayo Clin. **18**:165, 1943.

The latter condition had existed for twenty years prior to the development of the two superimposed conditions.

An autopsy study by Saphir and Parker [217] on the linitis plastica type of carcinoma was undertaken to see whether the investigation of a large amount of autopsy material would disclose diseases other than carcinoma which might cause linitis plastica. They arrived at the conclusion that it is questionable whether linitis plastica, in the sense of a purely inflammatory lesion, exists. No single instance was observed among 6,520 autopsies. In the 26 cases of carcinoma of the stomach of the linitis plastica type, careful histologic studies were made, and the details are given in the article, the chief characteristics being the presence of subacute and chronic inflammation, with much fibrosis and hyalinization. An important clinical fact brought out is the notation that the interval between the onset of symptoms referable to gastric disorders and death in these cases was uncommonly short as compared with that in the control group of cases of miscellaneous gastric carcinomas; also, that the postoperative survival period of 15 patients who were operated on seemed extremely short, eleven days or less.

An important estimate of the prognosis and end results in the treatment of cancer of the stomach is to be found in an article by Walters, Gray and Priestley.[218] In a series of 10,890 cases observed at the Mayo Clinic slightly more than half the patients were considered to be operable, a figure that in recent years has risen to about two thirds of those presenting themselves with this malady. About one quarter of the patients in the large series considered operable were found to have removable lesions, although in 1942 this was true of only one third of the number. The recent mortality rate was just under 11 per cent. Of those patients who underwent resection and survived the immediate postoperative period, nearly 30 per cent were alive at the end of five years, and over 6 per cent lived twenty-five years or longer. These figures show the increasingly favorable prognosis for this serious disease once the diagnosis is established.

The results of surgical treatment for cancer of the cardiac end of the stomach have been immeasurably improved since the introduction of transthoracic resection of these tumors. Churchill and Sweet [219] report 21 cases in which a tumor at the junction of the stomach and the esophagus was operated on by the transthoracic approach. Resection of the growth was done in 13 cases, with an esophagogastric anastomosis in 11; 8 patients were well and free of symptoms from two months to two and one-half years after the operation.

A rather surprising record of surgical success in the treatment of cancer of the stomach in aged persons is presented by Bowers.[220] He reports operative procedures on 104 persons who were over 60 years of age. The mortality rate following resection was 9 per cent for those over 60 From a study of 9 illustrative cases, Bowers believes that far from hopeless results may be anticipated in aged patients with carcinoma of the stomach, and that with early recognition of the condition and proper preparation, operation can be safely done with results, if anything, better than in younger age groups. That the most radical form of gastric

217. Saphir, O., and Parker, M. L.: Linitis Plastica Type of Carcinoma, Surg., Gynec. & Obst. **76**:206, 1943.

218. Walters, W.; Gray, H. K., and Priestley, J. T.: Prognosis and End Results in the Treatment of Cancer of the Stomach, Arch. Surg. **46**:939 (June) 1943.

219. Churchill, E. D., and Sweet, R. H.: Transthoracic Resection of Tumors of the Stomach and Esophagus, Ann. Surg. **115**:897, 1942; **116**:566, 1942.

220. Bowers, R. F.: The Surgical Treatment of Carcinoma of the Stomach in Aged Individuals, Surgery **11**:869, 1942.

operation is possible in the aged is evident from the report of Gillespie,[221] who operated on a man of 79 for carcinoma of the stomach and performed a total gastrectomy. The patient made an uneventful convalescence.

Less than 150 cases of true total gastrectomy for cancer have been reported. That such an operation is consistent with a relatively long survival period is evident from 2 cases reported by Joll and Adler.[222] Survival times of three years and two months, and two years and six months are reported in 2 of these authors' cases, in which the entire stomach, including the distal portion of the esophagus and the proximal portion of the duodenum, was removed because of cancer.

For patients considered inoperable, radiation therapy may achieve palliation of symptoms. Raven [223] reports 34 cases in which the disease was so advanced that only palliative measures were possible. Radon seeds were implanted in the growth at laparotomy, and the abdomen was closed without drainage. Radiation sickness was common owing to the close proximity of other vital organs, but life was apparently prolonged well beyond the period that would have been expected had the patients received no treatment. Symptoms were relieved in many instances. Three patients survived more than one year.

Acute perforation of gastric cancer is relatively uncommon. By 1935, about 80 cases had been reported. García Barón [224] was able to find only 3 perforations of cancer in a twelve year period, although at the same time 400 cases of perforated ulcer were encountered. Surgical intervention with closure is the obvious procedure.

A curious clinical note is that of Cardon,[225] who tells of a case of intractable generalized pruritus of three years' duration in an elderly person in whom carcinoma of the stomach was finally discovered. The itching of the skin was cured by successful surgical removal of the cancer.

Certain fundamental metabolic studies on patients with cancer of the gastrointestinal tract have been made by Ariel and his collaborators.[226] In one reported study 6 patients with neoplastic lesions of the extremities were used as controls and 6 patients with gastrointestinal cancer were studied by means of the aminoacetic acid tolerance test. Delayed absorption of aminoacetic acid followed the ingestion of 25 Gm. of that amino acid, and high peaks of plasma amino acid nitrogen curves were obtained for patients with gastric cancer, which suggest a delayed rate of utilization. After removal of the stomach from a patient with a gastric cancer, a rapid high peak of the plasma amino acid curve was obtained; this indicates that the presence of the cancer contributed to the slow absorption but not to the impaired utilization of aminoacetic acid. The defective absorption and metabolism of the end product of protein digestion in patients with gastric cancer may contribute to the hypoproteinemia so frequently exhibited by these patients. In another article, the authors conclude that patients with gastrointestinal

221. Gillespie, M. G.: Gastrectomy for Carcinoma: Case Report of Oldest Patient to Survive, Am. J. Surg. **57**:348, 1942.

222. Joll, C. A., and Adler, D. I.: Long Survival After Total Gastrectomy: A Brief Review with a Report of Two Cases, Brit. M. J. **2**:632, 1942.

223. Raven, R. W.: Inoperable Gastric Cancer: Treatment with Radon Seeds, Lancet **2**:335, 1942.

224. García Barón, A.: Acute Perforations of Malignant Tumors of the Stomach, Rev. clín. españ. **5**:96, 1942.

225. Cardon, L.: Generalized Pruritus Due to Carcinoma of the Stomach and Cured by Gastrectomy, Am. J. Digest. Dis. **10**:63, 1943.

226. Ariel, I.; Jones, F.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: XII. The Glycine Tolerance Test in Patients with Gastric Cancer, Ann. Surg. **117**:740, 1943. Abels, J. C.; Ariel, I.; Rekers, P. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Abnormalities in Patients with Cancer of the Gastrointestinal Tract: A Review of Recent Studies, Arch. Surg. **46**:844 (June) 1943.

carcinoma suffer from several metabolic abnormalities which may endanger their operative and postoperative course. Many of these abnormalities probably are related to hepatic insufficiency, which probably is induced by the presence of the gastrointestinal neoplasm. The removal of the cancer often is followed by a disappearance of the metabolic dyscrasias, principally that which involves the fabrication of serum protein. However, hypoproteinemia is a frequent occurrence and may persist well into the postoperative period. Total, and perhaps subtotal, gastric resection, although necessary for the surgical treatment of the patient, may institute a new metabolic disturbance, steatorrhea and consequent loss of weight. The importance of replacement therapy for such conditions is obvious.

Noncancerous Tumors of the Stomach.—Because of the relatively infrequent occurrence of noncancerous tumors of the stomach and the difficulties inherent in their diagnosis, reference will be made to the following articles. Multiple gastric polyps present no characteristic symptoms, but epigastric pain and tenderness appear to be rather common, and bleeding occurs as a frequent concomitant. A total of 121 such cases culled from the literature is reviewed by Pearl and Brunn.[227] Symptoms of pyloric obstruction were encountered, and several patients had noted symptoms over more than twenty years. The condition was frequently overlooked by the roentgenologist. Malignant degeneration was common.

The existence of diarrhea in association with a benign tumor of the stomach has been frequently noted. Proof that the gastric lesion is the cause of the intestinal symptom, however, is usually not possible. Culver and his associates[228] cite the case of a woman of 35 who complained of persistent diarrhea for one year prior to the diagnosis of a benign polypoid tumor of the stomach. Surgical resection was followed by good recovery and complete cessation of symptoms.

The relatively frequent occurrence of gastrointestinal bleeding in the presence of intraluminal tumors of the stomach is emphasized by Sahler and Hampton[229] in an excellent article dealing principally with the diagnostic features to be shown by the roentgenologist. The discussion is based on a study of 24 intramural gastric tumors, including leiomyoma, leiomyosarcoma, fibroma, fibrosarcoma and lymphoma. In all but 3 cases there were fairly adequate roentgen examinations. Bleeding was the most important common symptom. The diagnostic value of gastroscopy is stressed.

O'Donogue and Jacobs[230] review the literature on lymphosarcoma of the stomach, of which less than 500 cases have been recorded. A case report is given of a patient in whom an erroneous preoperative diagnosis was made of cancer of the stomach. The resected specimen showed reticulum cell sarcoma, a form constituting about half of all lymphosarcomas of the stomach. The authors conclude that lymphosarcoma constitutes from 1 to 2 per cent of all gastric malignant growths, that it occurs at an earlier period of life than does carcinoma, that it metastasizes late and that it responds more favorably to surgical removal than does carcinoma. Recognition of lymphosarcoma of the stomach secondary to a distant focus is difficult, but such recognition is important because of the wisdom

227. Pearl, F. L., and Brunn, H.: Multiple Gastric Polyposis: A Supplemental Report of Forty-One Cases Including Three New Personal Cases, Surg., Gynec. & Obst. **76**:257, 1943.

228. Culver, G. J.; Westinghouse, W., and Koenig, E. C.: Report of a Case of Benign Gastric Polyp Producing a Gastrogenic Diarrhea, Ann. Int. Med. **17**:1015, 1942.

229. Sahler, O. D., and Hampton, A. O.: Bleeding Associated with Extra Mucosal Tumor of the Stomach, Am. J. Roentgenol. **49**:442, 1943.

230. O'Donogue, J. B., and Jacobs, M. B.: Lymphosarcoma of the Stomach: Report of a Case with Some Clinicopathological Notations, Am. J. Surg. **58**:246, 1942.

of avoiding unnecessary surgical intervention in cases of this condition. Three cases, 1 of the authors' own, are reviewed by Buschke and Cantril.[231]

An extremely rare condition is reported by Selman,[232] who operated successfully on a benign tridermal teratoma in a child 4 months old.

A presentation by Lemmer [233] of the case of a 44 year old woman who was found to have a carcinoid tumor of the stomach is mentioned to call attention to the occurrence of a fairly common type of tumor in an uncommon location.

Unusual Tumors of the Small Bowel.—Nonulcerative disease of the duodenum is not particularly common, and in many instances anatomic variations from the normal, though demonstrable, produce no symptons. Certain conditions, however, are noted from time to time that are the cause of more or less serious symptoms and for this reason warrant mention. Congenital atresia of the duodenum is far from common, and successful surgical intervention for it is still rare. Ward and Cooper [234] report a successful duodenoduodenostomy on a newborn infant for atresia of the second portion of the duodenum. Only 14 instances of survival have been reported in the literature on this condition. The results of the operation were successful, and the clinical improvement in this case is in marked contrast to the result of any kind of surgical treatment of so-called duodenal ileus. A similar example of the same condition is reported by Wiig and Clagett,[235] in which a successful posterior gastroenterostomy was performed on a 15 day old infant. Atresia was not absolutely complete in this instance and involved the lower portion of the duodenum. A third instance of complete atresia is reported by Impink and Clammer.[236] In this instance, a duodenojejunostomy performed fifty hours after birth was unsuccessful because of pulmonary complications.

Dilatation of the bowel and hypertrophy of its walls in the absence of obstruction or inflammation occur in cases of megacolon, but a similar condition in the small intestine is most unusual. Such a case is described by Brown and Pemberton.[237] Three years after an operation for a correctly diagnosed duodenal ulcer, a new type of abdominal distress, midabdominal pain not relieved by food, was observed, and a roentgen examination at this time showed slight dilatation of the distal portion of the duodenum. Because of the persistence of symptoms in spite of treatment, an operation was done, and an enteroanastomosis was made between the first part of the jejunum, which was dilated, and a normal lower portion. After the operation symptoms continued and vomiting increased. Roentgen examination after a barium sulfate meal showed dilatation of the entire jejunum, more marked than before operation. Subsequently a third operation was performed, with resection of 78 cm. of enormously dilated jejunum. The specimens showed subacute jejunitis with multiple ulcerations. It could not be determined whether the abnormal condition of the duodenum and jejunum was a primary dilatation and hypertrophy or whether it was an inflammatory process.

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231. Buschke, F., and Cantril, S. T.: Secondary Lymphosarcoma of the Stomach, Am. J. Roentgenol. **49**:450, 1942.

232. Selman, A. N.: Complex Tridermal Teratoma of the Stomach (Benign): Case Report, Am. J. Surg. **59**:567, 1943.

233. Lemmer, K. E.: Carcinoid Tumors of the Stomach, Surgery **12**:378, 1942.

234. Ward, C. S., Jr., and Cooper, F. W., Jr.: Atresia of the Duodenum: Case Successfully Treated by Duodenoduodenostomy, Ann. Surg. **117**:718, 1943.

235. Wiig, L. M., and Clagett, O. T.: Congenital Atresia of the Duodenum: Report of a Case, Proc. Staff Meet., Mayo Clin. **17**:577, 1942.

236. Impink, R. R., and Clammer, G. R.: Atresia of the Duodenum: Case Report. Ann. Surg. **116**:334, 1942.

237. Brown, P. W., and Pemberton, J. DeJ.: Megaduodenum and Megajejunum. Proc. Staff Meet., Mayo Clin. **18**:109, 1943.

An exceedingly rare cause of pain arising from partial obstruction in the duodenum is described by Brooks and Weinstein.[238] Nausea, vomiting and questionable jaundice caused the patient to enter the hospital fifteen years after an acute cholecystitis with drainage. The recurrent attacks of nausea and vomiting prior to his admission at this time were thought to be due to a peptic ulcer, but because of the severity of the symptoms exploration was done. The first 2 feet (60 cm.) of the jejunum showed marked hypertrophy and dilatation. One inch (2.5 cm.) from the pylorus was a large polypoid mass, which when delivered through the incision in the duodenum was found to be attached to the posterior wall of the descending portion of the duodenum. The tumor appeared to be a cyst of the ampulla of Vater, with symptoms due to intussusception of the cyst.

An equally unusual cause for vague epigastric distress associated with diarrhea and occult blood in the stools is described by Shackleford and his associates.[239] At operation the patient was found to have metastatic myosarcoma of the ampullary portion of the duodenum. She had had a myosarcoma of the uterus removed four years before. The operation was immediately successful.

Carcinoma of the duodenum has been reported from time to time but is infrequent enough to warrant mention. Three cases are reported: 1 case of carcinoma of the duodenal bulb, and 2 of carcinoma involving the third (infrapapillary) portion of the duodenum, by Hartzell,[240] Berger and Koppelman [241] and Duff and his associates,[242] respectively. The majority of such tumors are around the papillae of Vater.

Three cases of primary adenocarcinoma of the jejunum (Sangster [243]; Kahn and Bay [244]) may be added to the gradually increasing list of these rather uncommon tumors.

The roentgen diagnosis of lesions involving the ileum, the cecum and the proximal portion of the ascending colon is discussed by Pendergrass and Chamberlin.[245] The authors present a few instances in which the clinical and roentgen findings were equivocal as regards the diagnosis of early lesions involving this area. They suggest certain points noted in their cases, which may be of aid in the proper analysis of similar problem cases. Three methods of study are described as ways of arriving at a precise diagnosis: roentgen examination after a barium sulfate meal, examination after an opaque double contrast enema, and study of the intestine with the Miller-Abbott tube.

Only in recent years has it been recognized that argentaffine tumors may produce clinical symptoms and assume all the properties of malignant growths. It is not generally accepted that carcinoid tumors arise from the crypts of Lieberkühn. These cells are found throughout the gastrointestinal tract but are most abundant in the appendix and the terminal portion of the ileum. Interesting case

238. Brooks, B., and Weinstein, A.: Cyst of Ampulla of Vater: Case Report, Ann. Surg. **117**:728, 1943.

239. Shackleford, R. T.; Fisher, A. M., and Firor, W. R.: Duodenal Tumor of Unusual Character, Ann. Surg. **116**:864, 1942.

240. Hartzell, H. V.: A Case of Carcinoma of the Duodenal Bulb Diagnosed Preoperatively, Radiology **39**:474, 1942.

241. Berger, L., and Koppelman, H.: Primary Carcinoma of the Duodenum, Ann. Surg. **116**:738, 1942.

242. Duff, G. L.; Foster, H. L., and Bryan, W. W.: Primary Carcinoma of the Infra-Ampullary Portion of the Duodenum, with Example of Probable Origin from Aberrant Pancreatic Tissue, Arch. Surg. **46**:494 (April) 1943.

243. Sangster, A. H.: Case of Adenocarcinoma of the Jejunum, Brit. M. J. **1**:12, 1943.

244. Kahn, M., and Bay, M. W.: Carcinoma of the Jejunum, Am. J. Surg. **58**:145, 1942.

245. Pendergrass, E. P., and Chamberlin, G. W.: The Roentgen Diagnosis of Lesions Involving the Ileum, Cecum and Proximal Ascending Colon, Am. J. Roentgenol. **48**:16, 1942.

reports of single and multiple tumors of this nature by Pennington and Priestley,[246] Miller and Herrmann [247] and Gold and Grayzel [248] may be mentioned.

Records of other rare tumors of the small intestine include cases of hemangioma of the ileum,[249] metastatic melanotic sarcoma of the ileum [250] and primary Hodgkin's sarcoma of the jejunum.[251] In addition to several individual case reports of primary lymphosarcoma,[252] a fairly complete discussion of this type of disease is presented by Usher and Dixon [253] and by Weber, Kirklin and Pugh.[254] The incidence of lymphosarcoma is discussed, over one third of the growths being found in the jejunum and ileum and the remainder in the colon. Colicky pain, loss of weight, anemia and a palpable abdominal mass are fairly characteristic symptoms. Ulcer and perforation are rare and intussusception infrequent. Chronic or subacute obstruction is not uncommon; this is not surprising, since the average diameter of the tumors reported is between 5 and 10 cm. The best prognosis seems to be for lymphosarcoma of the cecum. The details of roentgenologic diagnosis are included in the second article mentioned, but the authors are careful to conclude that they can offer no suggestions as to how roentgenologically to distinguish lymphoblastoma from other lesions of the gastrointestinal tract.

Regional Ileitis.—The consensus at present seems to be that regional ileitis is essentially a surgical disease. The diagnosis is dependent almost entirely on adequate roentgenologic studies, although the clinical course at times is very suggestive. Both Sussman and Wachtel [255] and Strömbeck [256] emphasize striking differences in the picture obtained in the acute and chronic phases. The former authors believe that roentgenologic differentiation from a deficiency pattern is difficult in the acute phase of the disease, but Strömbeck states flatly that acute ileitis has a characteristic roentgen picture. The latter describes the findings in detail and states that in acute ileitis the outline of the mucous membrane in the last 10 to 15 cm. of the ileum is uneven and edematous. The mucosal swelling is most pronounced next to Bauhin's valve, the two lips of which sometimes are considerably swollen and bulge into the cecum. The mucosal relief in the terminal portion of the ileum is high and irregular, and a walnut-sized filling defect is seen at the site of the valve. He states that roentgen examination can be of great value in differentiating acute appendicitis from acute simple terminal ileitis in

246. Pennington, R. E., and Priestley, J. T.: Multiple Carcinoid Tumors of Small Intestine: Report of Case, Proc. Staff Meet., Mayo Clin. **18**:49, 1943.

247. Miller, E. R., and Herrmann, W. W.: Argentaffin Tumors of the Small Bowel, Radiology **39**:214, 1942.

248. Gold, I. R., and Grayzel, D. M.: Multiple Argentaffinomas in Ileum with Metastases in Lymph Nodes and in the Liver, Am. J. Surg. **60**:144, 1943.

249. Christopher, F.: Hemangioma of the Ileum, Ann. Surg. **116**:945, 1942.

250. Phillips, J. R.: Metastatic Melanotic Sarcoma to the Ileum Causing Intussusception, Am. J. Digest. Dis. **10**:147, 1943.

251. Badia, P. D.: Primary Hodgkin's Sarcoma of the Jejunum with Perforation, Resection and Radiotherapy Case, Am. J. Surg. **59**:577, 1943.

252. Charache, H.: Primary Lymphosarcoma of the Intestine in a Boy of Seven: Follow-Up Nine Years, Am. J. Surg. **59**:601, 1943. Borden, D. L., and Taylor, F. D.: Primary Lymphosarcoma of the Small Intestine: Case Report, Mil. Surgeon **92**:255, 1943. Menne, F. R.; Mason, D. G., and Johnston, R.: Lymphosarcoma of the Intestine: Report of Two Cases, Arch. Surg. **45**:945 (Dec.) 1942.

253. Usher, F. C., and Dixon, C. F.: Lymphosarcoma of the Intestines, Gastroenterology **1**:160, 1943.

254. Weber, H. M.; Kirklin, B. R., and Pugh, D. G.: Lymphoblastoma Primary in the Gastrointestinal Tract, Am. J. Roentgenol. **48**:27, 1942.

255. Sussman, M. L., and Wachtel, E.: Granulomatous Jejuno-Ileitis, Radiology **39**:48, 1942.

256. Strömbeck, J. P.: Terminal Ileitis and Its Roentgen Picture, Acta radiol. **22**:827, 1941.

children and young people, but it is probable that most clinicians would prefer to avoid the use of barium sulfate under such acute conditions. The chronic stenosing form of the disease is more easily diagnosed in most instances, except when it is necessary to rule out ileocecal tuberculosis.

Ginzburg and Garlock [257] state that much of the confusion surrounding indications for therapy (medical versus surgical treatment) of this disease arises from the failure to differentiate between the localized form, which is confined to the distal 4 or 5 feet of ileum, and the more generalized type, in which the distal involvement is only part of a generalized enteritis. They suggest that the term "distal ileitis" be substituted for "regional ileitis," and they believe that this type is essentialy amenable to surgical treatment. On the basis of their own experience, they believe that the symptoms of "distal ileitis," as a rule, are markedly ameliorated by ileocolostomy with exclusion, rather than resection. Lahey and Sanderson [258] definitely prefer radical resection for the ileum, ascending colon and hepatic flexure as the treatment of choice, and this view is generally held among surgeons.

A plea for conservatism in the surgical management of acute regional enteritis is voiced by Smithy,[259] who reports on a small group of patients managed by simple exploration and appendectomy. None showed progression of the disease. He states, as do others, that a strong tendency toward spontaneous healing is present in certain instances of acute regional enteritis, and he advocates conservative management in many cases. He makes the reasonable suggestion that in order to detect the occasional case in which there is a tendency for the condition to progress to chronic regional enteritis, conscientious observation and frequent postoperative roentgen study are essential in cases of acute enteritis managed by simple exploration and appendectomy.

In Crohn's extensive experience, this disease almost invariably begins in the distal part of the ileum and progresses proximally. For this reason, the report by Johnson [260] is of interest. In his case, the patient, a Negro, had progressive symptoms leading to operation, which showed multiple areas of involvement from that portion of the jejunum just below the ligament of Treitz, extending down for some distance in the upper part of the jejunum. Apparently the disease progressed distally and produced symptoms of obstruction but remained localized to a relatively short segment, even after a six-year period. Crohn comments on this case as being unusual and cites another reported from China.

Studies on absorption of fat and of vitamin A in sprue and in jejunoileitis by Adlersberg and Sobotka [261] suggest a basic difference in fat absorption between sprue and inflammatory disease of the small intestine. In contrast to persons with sprue, patients with extensive granulomatous jejunoileitis had a fairly satisfactory absorption of fat and of vitamin A, and because of this fact the authors believe that in certain borderline cases in which the differential diagnosis is difficult an additional diagnostic point is available.

Relatively little attention has been given in the literature to anorectal findings in cases of regional ileitis. In the article by Sussman and Wachtel, already

257. Ginzburg, L., and Garlock, J. H.: Regional Ileitis, Ann. Surg. **116**:906, 1942.

258. Lahey, F. H., and Sanderson, E.: Lesions of the Right Colon Involving Right Colectomy, J. A. M. A. **120**:1356 (Dec. 26) 1942.

259. Smithy, H. G.: Conservation in the Surgical Management of Acute Regional Enteritis, Surgery **13**:122, 1943.

260. Johnson, W. R.: Chronic, Non-Specific Jejunitis with Unusual Features, Gastroenterology **1**:347, 1943.

261. Adlersberg, D., and Sobotka, H.: Fat and Vitamin A Absorption in Sprue and Jejuno-Ileitis, Gastroenterology **1**:357, 1943.

alluded to, 1 instance is reported in which inflammation was seen proctoscopically. Jackman and Smith [262] review 114 consecutive cases of regional ileitis in which the diagnosis was made by roentgenologic examination confirmed by exploration and in which sigmoidoscopic examinations were made. Ulceration of the lower part of the bowel was found after short-circuiting operations. One third of the patients had an anal abscess or an anal fistula or gave a history of having had an operation for a fistula, the ileitis remaining undiscovered until a later date. In almost one fifth of the cases an extrarectal mass was found; in 8 cases anal ulceration or a contracted anal outlet was found; 4 patients had ulceration of the lower part of the bowel after short-circuiting operations and resection of the diseased portion of the bowel. The combination of an anal abscess or fistula and vague intestinal disturbances in a young adult should make the clinician suspect the possibility of regional ileitis.

262. Jackman, R. J., and Smith, N. D.: Some Manifestations of Regional Ileitis Observed Sigmoidoscopically, Surg., Gynec. & Obst. **76**:444, 1943.

(To Be Continued)

News and Comment

GENERAL NEWS

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.—Eighteen applications for grants were received by the Trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1943. Thirteen of these came from the United States and the other five from five different countries in Europe, Asia and North and South America.

In the twenty years of its existence the Foundation has made four hundred and eighty-one grants, which have been distributed to scientists throughout the world.

The purposes for which the Fund may be used are mentioned in the January 1942 issue of the ARCHIVES, page 159.

Applications for grants to be held during the year 1944-1945 should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston, and must be in his hands before April 1944. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, include an accurate description of the research and give the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done.

SOCIETY NEWS

Mississippi Valley Medical Society.—The tenth annual meeting of the Mississippi Valley Medical Society will be held at the Pere Marquette Hotel, Peoria, Ill., September 27 and 28.

Scientific exhibits will be a feature of the meeting.

The officers recently elected are: president, Dr. C. Paul White, Kewanee, Ill.; president elect, Dr. Grayson L. Carroll, St. Louis; first vice president, Dr. Milton E. Bitter, Quincy, Ill.; second vice president, Dr. E. A. Cunningham, Louisiana, Mo.; third vice president, Dr. Con R. Harken, Osceola, Iowa; secretary-treasurer, Dr. Harold Swanberg, Quincy, Ill. The members of the Board of Directors are: from Illinois, Drs. Charles Harmon (Springfield), G. A. Sihler Jr. (Litchfield), L. H. Sloan and C. C. Maher (Chicago), E. F. Parker (Moline), E. E. Nystrom (Peoria) and Ralph McReynolds (Quincy); from Missouri, Drs. F. J. Tainter and Clyde Dyer (St. Louis), and W. F. Francka (Hannibal); from Iowa, Drs. F. A. Hennessy (Calmar), J. H. Randall (Iowa City) and B. J. Dierker (Fort Madison).

The society has established an endowment fund, which is already a going affair, with a $500 appropriation. All contributions to the fund will be invested in war bonds. A new plan for life membership, whereby the fee paid will depend on the applicant's age, has been adopted, and new, attractive certificates of life membership have been authorized. All fees for life memberships will be placed in the endowment fund, and hence in war bonds.

The January issue of the *Mississippi Valley Medical Journal*, called the "Chicago Number," contains some of the contributions by physicians of Chicago which were presented at the meeting of the society held in Quincy, Ill., last year. The rest of the papers will appear in the April issue, which will be called the "War Medicine Number" and will feature a symposium on war medicine.

Correspondence

CLINICAL SIGNIFICANCE OF GLYCOGEN CONTENT OF LIVER

To the Editor:—In order to prevent an erroneous impression, I wish to draw attention to some pertinent omissions from a paper by Dr. Morton Korenberg entitled "Clinical Significance of Glycogen Content of Liver," in the December issue (ARCH. INT. MED. **72**: 746, 1943).

The studies which provided the data presented in this paper were made in the May Institute for Medical Research, the University of Cincinnati, and the Research Foundation of the Children's Hospital, Cincinnati. These studies were performed by Dr. Waldo E. Nelson, Dr. Norton Nelson and me. Dr. Korenberg, serving in the capacity of an intern, participated in some of the clinical studies and was recognized for this work as a junior author of a report entitled "The Hepatic Glycogen Reserves in Diabetes Mellitus" *(Endocrinology* **28**:358, 1941). Subsequently, studies by E. Perry McCullough and his co-workers utilized the phlorhizin procedure as presented in the aforementioned report.

Many of the data, comments and interpretations which appear in Dr. Korenberg's paper were previously presented in the aforementioned report and in lectures to which Dr. Korenberg had access. The remainder of the data which are presented in his paper were made available to him three years ago, when he prepared a thesis for a graduate degree. Permission to publish these data was neither requested nor granted.

No reference to these facts exists in Dr. Korenberg's paper, an omission which makes it necessary for me to draw attention to the institutions in which the work was done and the investigators who did it.

MAJOR I. ARTHUR MIRSKY, M.C.,
Army of the United States.
The May Institute for Medical Research,
Cincinnati (on leave of absence in military service).

VALUE OF DETERMINATION OF UROBILIN

To the Editor:—In the June 1943 number of the ARCHIVES OF INTERNAL MEDICINE, in the review of my book "La urobilina en el estado normal y patológico," it is said: "The book, alas, definitely puts an end to the hopes of both investigator in clinical laboratories and clinician that urobilin, so tempting to test for, is of any practical clinical diagnostic value."

One of the more important conclusions at which I arrive in that discussion, however, is quite opposite to the reviewer's opinion. I definitely show that it has been proved by the experiments reported on that quantitative measuring of urobilin in urine or in blood (when present) is of considerable value for estimation of hepatic function. Quantitative determination of urobilin in bile is of distinct importance in the diagnosis of cholecystitis, and its measurement in feces is undoubtedly beneficial in certain special cases.

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Book Reviews

Publicaciones del Centro de Investigaciones Tisiologicas, Hospital Tornu, Buenos Aires, Argentina. Volume VI, 1943.

The sixth volume of the research studies of the Center of Investigation of the Tornu Hospital, under the direction of Prof. Roque A. Izzo, reflects a high caliber of work. Although it is essentially the product of a tuberculosis organization, including a painstaking hematometric study on normal and on tuberculous subjects by Mora and various pathologic studies of tuberculosis, cancer and miscellaneous topics by other members of the staff, the studies on the vitamin B complex by Costoya are outstanding in extent and thoroughness. After a painstaking review of the history, discovery, chemical constitution, preparation, pharmacology and standardization of the complex, the author focuses attention on methods of analysis and their practical application.

Although many principles have been used in analysis for vitamin B, the author was able to use the fluorescence produced by thiochrome developed from thiamine in blood and urine as a means of determining it. The readings were made in a Pulfrich photometer with an ultraviolet source of light. In a series of cases there were found averages of 15.04 and 31.66 micrograms per hundred cubic centimeters of blood and of urine respectively.

The studies on the vitamin B complex will be useful to biochemists, research workers, clinicians and clinical pathologists. The other reports are more for pathologists or persons engaged in research in tuberculosis.

The binding is heavy paper; the illustrations are good, and the paper, printing and type are excellent.

A Hundred Years of Medicine. By C. D. Haagensen and Wyndham E. B. Lloyd. Price, $3.75. Pp. 443, with 42 illustrations. New York: Sheridan House, 1943.

This is an interesting bit of light reading that will serve to pass the time of the physician if he can find any idle moments these days. It is not a serious attempt to publish a history of medicine. The authors have given a short synopsis of medicine up to a hundred years ago. Then they have selected what appear to them to be the important advances during the past hundred years in medicine and surgery and in the social aspects of medicine. The nurses have not been entirely neglected. One might quibble a bit about the complete accuracy of some of the statements, and one might also raise a question about the wisdom of the selection of material in some instances. If either of these objections is valid, they constitute a reason for not putting this material before the lay reader. The material is rather technical for the lay reader to understand well. However, he must be greatly confused by much of the material that is directed at him in these days, and a little additional confusion will not do him irreparable harm. The jacket that surrounds the book states that both authors are physicians. According to this source of information Dr. Haagensen is a surgeon and pathologist on the faculty of Columbia University's School of Medicine and Dr. Lloyd is a specialist in public health working in England.

Synopsis of Tropical Medicine. By Sir Philip Manson-Bahr, M.D., Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine. Price $2.50. Pp. xii + 224, with 5 plates. Baltimore: Williams & Wilkins Company, 1943.

The author states that this small volume was written in response to numerous requests to provide a guide to tropical medicine in a condensed form, suitable for medical officers and others whom the exigencies of the moment call to the tropics. It is of proper size to fit into one's pocket, and everything that it says is condensed in similar fashion.

The tropical diseases have been grouped under their causes: protozoal diseases, rickettsial diseases, bacterial diseases, virus diseases, fungous diseases, nutritional diseases, etc. Each disease is discussed according to much the same pattern—its cause, pathologic picture, clinical features, diagnosis, treatment and prevention. The whole story is told in a few lines. At the end is an excellent index, so that the perplexed physician can readily look up anything from A. L. 63 (if he wishes a preventive powder against lice) to zygote (if he is concerned with malaria).

It is remarkable to find such a complete handbook in such small compass. The author says that it represents, on his part, a small contribution to the war effort. Many physicians and students will be grateful to him for making it.

Borderlands of Psychiatry. By Stanley Cobb, M.D. Price $2.50. Pp. 166. Cambridge, Mass.: Harvard University Press, 1943.

This little brochure represents a series of essays on subjects that have special interest to the author, to quote the introduction. Cobb has prepared a splendid summary, it might be called, of many features of psychiatry that touch on the practice of every physician. The material represents special studies made by himself and others; it contains a certain number of illustrative case reports. Admixed with the scientific presentation there is a philosophic angle to Cobb's writing which adds much to the intellectual enjoyment of the material.

The essays are so well written and splendidly expressed that they make for easy reading while one is absorbing the psychosomatic point of view of the present day.

The Arthropathies. By Alfred A. de Lorimier. Price $5.50. Pp. 319, with 678 figures. Chicago: Year Book Publishers, Inc., 1943.

This little book is really an atlas of the roentgenologic changes in the joints in various diseases. There are nearly seven hundred reproductions of films, illustrating all phases of the subject, together with concise descriptive notes. Unfortunately, some of the reproductions do not show up too well, and others are marred by the extraordinary method used to point out the lesions, which covers the cuts with letters and zigzag arrows. Figure 311 is a good example.

The Dysenteric Disorders. By Sir Philip Manson-Bahr, M.D., Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, with an appendix by W. John Muggleton, M.S.M. Second edition. Price $10. Pp. xiv + 629, with 23 plates and 108 figures. Baltimore: Williams & Wilkins Company, 1943.

The first edition of this book was reviewed shortly after its appearance in 1939 (*J. A. M. A.* **114:**1010 [March 16] 1940). It was regarded as a comprehensive description of the result of the author's experience in the tropics and his extensive practice in the Hospital for Tropical Diseases in London.

The second edition is much like the first. It is readable and has a fine bibliography. Medical officers and students will find it a particularly useful handbook, which gathers together current knowledge of the dysenteric disorders in a pleasant and instructive manner.

A Synopsis of Clinical Syphilis. By James Kirby Howles, M.D., M.M.S., Professor of Dermatology and Syphilology and Director of the Department, Louisiana State University School of Medicine. Price, buckram, $6.00. Pp. 671, with index; illustrated. St. Louis: C. V. Mosby Company, 1943.

Section I of the book is devoted to general considerations of etiology, pathology, classification, symptomatology, diagnosis and treatment; section II, to systemic and regional syphilis, and the final section, to problems of the familial and public health aspects of the disease. The appendix comprises historical notes on the condition. There is also a comprehensive bibliography alphabetically arranged.

The work is well organized, moderately condensed and well presented. There are numerous well selected illustrations. The reviewer has no hesitancy in recommending this book to students and practitioners of medicine.

Your Arthritis: What You Can Do About It. By Alfred E. Phelps, M.D. Price, cloth, $2.00. Pp. 192, with index; illustrated. New York: William Morrow and Company, 1943.

This book was written for the laity with a twofold purpose: to tell the arthritic patient how best to cooperate with his own physician during treatment and to relieve his physician from the arduous, time-consuming task of giving detailed instructions concerning all the little things the patient can do to get the most out of life with the limitations imposed by the disease.

The views expressed represent the consensus of the leading rheumatologists in this country. There are no misstatements of fact, and the purpose of the work is admirably carried out.

Manometric Methods as Applied to the Measurement of Cell Respiration and Other Problems. By Malcolm Dixon, with a foreword by Sir F. G. Hopkins. Second edition. Price $1.75. Pp. 157, with 20 figures. New York: The Macmillan Company, 1943.

This book discusses in detail the technical aspects of apparatus and procedure used in measuring the rate at which an isolated tissue consumes oxygen and produces carbon dioxide. Although it is likely to interest the general reader as illustrating the high degree of refinement that has been attained in this field of scientific work, it is intended simply for use in research laboratories where the respiration of cells and tissues is being studied; the diagrams, tables and bibliography make it an excellent book for this purpose.